

EFFECTS OF OPIOIDS ON VENTILATION AND HEMODYNAMICS

Leena Mildh

Helsinki 2007

Department of Anesthesiology and Intensive Care Medicine
University of Helsinki,
Helsinki, Finland

EFFECTS OF OPIOIDS ON VENTILATION AND HEMODYNAMICS

Leena Mildh

Academic Dissertation

To be presented with the permission of the Faculty of Medicine, University of Helsinki,
for public examination in the Auditorium XII, Unioninkatu 34, University of Helsinki,
Helsinki, on May 5th, 2007 at 10 a.m.

Helsinki 2007

Supervisors:

Professor Per Rosenberg
Department of Anesthesiology and Intensive Care Medicine
University of Helsinki
Helsinki, Finland

Docent Olli Kirvelä
Department of Anesthesiology and Intensive Care Medicine
Helsinki University Central Hospital
Helsinki, Finland

Reviewers:

Professor Olli Polo
Department of Respiratory Medicine
University of Tampere
Tampere, Finland

Docent Päivi Valta
Department of Anesthesiology and Intensive Care Medicine
Jorvi Hospital
Helsinki University Central Hospital
Espoo, Finland

Official opponent:

Professor Klaus Olkkola
Department of Anesthesiology and Intensive Care
University of Turku
Turku, Finland

ISBN 978-952-92-2008-3 (paperback)
ISBN 978-952-10-3903-4 (pdf)

Helsinki University Printing House
Helsinki 2007

Contents

1	LIST OF ORIGINAL COMMUNICATIONS	8
2	ABBREVIATIONS	9
3	ABSTRACT	11
4	INTRODUCTION	13
5	REVIEW OF LITERATURE	15
5.1	Opioid receptors mediating respiratory depression	15
5.2	Respiratory effects of opioids	16
5.2.1	Morphine	17
5.2.2	Oxycodone	17
5.2.3	Pethidine	18
5.2.4	Fentanyl.	18
5.2.5	Alfentanil	19
5.2.6	Tramadol	20
5.3	Hemodynamic effects of opioids	20
5.3.1	Morphine	22
5.3.2	Oxycodone	22
5.3.3	Pethidine	22
5.3.4	Fentanyl.	23
5.3.5	Alfentanil	23
5.3.6	Tramadol	23
5.4.	Histamine release by opioids	23
5.5	Catecholamine release by opioids	24
5.6	Other opioids	25
5.7	Ketamine	25
5.8	Effect of pain on breathing and hemodynamics	26
5.9	Effect of oxygen on breathing	27
5.10	Respiratory measurements.	27
5.10.1	Measurements of resting ventilation	27
5.10.1.1	Analysis of breathing pattern	27
5.10.1.2	Pneumotachometry	28

5.10.1.3	Airway occlusion pressure	28
5.10.1.4	Respiratory inductive plethysmography	28
5.10.2	Ventilatory challenges	29
5.10.3	Measurements of gas exchange	29
5.10.3.1	Indirect calorimetry	29
5.10.3.2	Blood gas analysis	30
5.10.3.3	Alveolar ventilation	30
6	AIMS OF THE STUDY	31
7	SUBJECTS AND METHODS	32
7.1	Volunteers and patients	32
7.2	Ethical aspects	32
7.3	Study design	32
7.4	General considerations	35
7.5	Study drugs	35
7.6	Measurements	36
7.6.1	Respiratory monitoring	36
7.6.1.1	Respiratory inductive plethysmography	36
7.6.1.2	Arterial blood gas analysis	37
7.6.1.3	Arterial hemoglobin oxygen saturation	37
7.6.1.4	Alveolar ventilation	37
7.6.2	Hemodynamic measurements	37
7.6.3	Measurements of gas exchange	37
7.6.4	Biochemical determinations	38
7.6.5	Computer controlled infusions	38
7.6.6	Pharmacodynamic modeling	38
7.6.7	Pain assessment	39
7.6.8	Subjective assessments	39
7.6.9	Radiological assessment	39
7.6.10	Statistics	40
8	RESULTS	41
8.1	Respiratory effects	41
8.1.1	Effects on ventilation (V_E and V_A)	41
8.1.2	Effects on breathing pattern	42

8.1.3 Effects on arterial blood gases43
8.1.4 Effects on arterial hemoglobin oxygen saturation43
8.2 Effects on gas exchange44
8.3 Hemodynamic effects44
8.4 Effects on plasma catecholamines44
8.5 Effects on plasma histamine.45
8.6 Effects on atelectasis formation45
8.7 Adverse effects45
9 DISCUSSION46
9.1 Discussion of methods46
9.1.1 Accuracy of respiratory inductive plethysmography46
9.1.2 Accuracy of indirect calorimetry.47
9.1.3 Reliability of pharmacodynamic modeling48
9.1.4 Suitability of methods used48
9.2 Discussion of the results49
9.2.1 Respiratory effects49
9.2.2 Hemodynamic effects53
9.2.3 Effects on gas exchange55
9.2.4 Effects on plasma catecholamines55
9.2.5 Effects on plasma histamine56
9.2.6 Effects on atelectasis formation57
9.2.7 Limitations of the present series of studies57
10 SUMMARY AND CONCLUSIONS.59
11 ACKNOWLEDGEMENTS60
12 REFERENCES62

1 LIST OF ORIGINAL COMMUNICATIONS

The present thesis is based on the following original communications, which are referred to in the text by their Roman numerals.

- I Mildh L, Taittonen M, Leino K, Kirvelä O. The effect of low-dose ketamine on fentanyl induced respiratory depression. *Anesthesia* 1998;53:965-970.
- II Mildh L, Leino K, Kirvelä O. The effects of tramadol and pethidine on respiratory mechanics, plasma catecholamine levels and haemodynamics on healthy volunteers. *J Clin Anesth*, 1999;11:310-316.
- III Mildh L, Tuomisto L, Scheinin M, Kirvelä O. Morphine-induced hemodynamic stimulation: the effects of two doses on healthy subjects. *Anesth Analg* 2000;91: 51–57.
- IV Mildh L, Scheinin H, Kirvelä O. Concentration-effect relationship of the respiratory depressant effects of alfentanil and fentanyl. *Anesth Analg* 2001;93:939–946.
- V Mildh L, Piilonen A, Kirvelä O. Supplemental oxygen is not required in trauma patients treated with iv opioids. *Am J Emerg Med* 2003;21:35–38.

The publishers of the original communications kindly granted their permission to reproduce the articles in this thesis.

2 ABBREVIATIONS

ANOVA	Analysis of variance
AVDO ₂	Arterio-venous oxygen difference
CT	Computer tomography
CP ₅₀	Drug concentration associated with 50% of peak drug effect
CNS	Central nervous system
CO	Cardiac output
CYP ₄₅₀	Cytochrome P 450
EC ₅₀	The concentration of a drug required to produce a specific effect in 50% of patients to whom it is administered
EEG	Electroencephalography
HR	Heart rate
i.v.	Intravenous(ly)
MAC	Mean alveolar concentration
MAP	Mean arterial blood pressure
NMDA	N-methyl-D-aspartate
ORL-1	Orphan opioid receptor
p.o.	Peroral(ly)
PaO ₂	Arterial blood oxygen partial pressure
PaCO ₂	Arterial blood carbon dioxide partial pressure
P _{0.1}	Airway occlusion pressure at 0.1 seconds
PT	Pneumotachometer
RC%	The proportion of ventilation that can be attributed to rib cage expansion
RIP	Respiratory inductive plethysmography
SD	Standard deviation
SpO ₂	Arterial blood hemoglobin oxygen saturation measured by pulse oximetry
T _E	Expiratory time
T _I	Inspiratory time
T _I /T _{TOT}	Inspiratory duty cycle
T _{TOT}	Duration of respiratory cycle
T _{Keo}	Time of equilibration between serum concentration and effect site concentration
V _A	Alveolar ventilation
VAS	Visual analogue scale
VCO ₂	Carbon dioxide production
V _E	Minute ventilation

V_D	Dead space ventilation
VO_2	Oxygen consumption
V_T	Tidal volume
V_T/T_I	Mean inspiratory flow

3 ABSTRACT

Opioids are most commonly used for treatment of severe pain. However, the fear of respiratory depression has restricted the use of opioids. Depending on the monitoring system used, different modes of opioid respiratory effects have been noted in previous studies. All opioids also cause alterations in hemodynamics at least to some extent. The main goal of this series of investigations was to elucidate the native ventilatory and hemodynamic effects of different opioids. Also, the effects of ketamine were studied in conjunction with an opioid causing respiratory depression. In order to avoid the interference of respiratory monitoring with the actual drug effect, a non-invasive monitoring system was chosen for this study.

Studies I–IV each involved 8 healthy male volunteers. Study V involved 13 patients with lower or upper extremity traumas. The opioids studied were morphine, oxycodone, pethidine, fentanyl, alfentanil, tramadol and ketamine. The respiratory parameters used in this study were breathing pattern measured with respiratory inductive plethysmography, gas exchange measured with indirect calorimetry, blood gas analysis and pulse oximetry. Hemodynamics was measured with arterial blood pressure, heart rate and oxygen consumption. Plasma catecholamine and histamine concentrations were also determined.

All opioids studied caused an alteration in respiratory function. Respiratory rate, alveolar ventilation and minute ventilation decreased, while tidal volume increased in most situations. Breathing pattern was also significantly affected after opioid administration. The respiratory depression caused by oxycodone was deeper than the one caused by same dose of morphine. An equianalgesic dose of tramadol caused markedly smaller respiratory depression compared to pethidine. The potency ratio for respiratory depression of fentanyl and alfentanil is similar to analgesic potency ratio studied elsewhere. Racemic ketamine attenuated the respiratory depression caused by fentanyl, if measured with minute ventilation. However, this effect was counteracted by increased oxygen consumption. Supplemental oxygen did not offer any benefits, nor did it cause any atelectasis when given to opioid treated trauma patients.

Morphine caused a transient hemodynamic stimulation, which was accompanied by an increase in oxygen consumption. This phenomenon was not noted with the use of intravenous oxycodone. Alfentanil, fentanyl, tramadol and pethidine infusions had minimal effects on hemodynamics. Plasma catecholamine concentrations were increased after morphine, oxycodone and pethidine administration. Plasma histamine concentrations were not elevated after morphine nor oxycodone administration.

Respiratory depression is a side effect noted with all opioids. The profile of this phenomenon is quite similar with different opioid-receptor agonists. The hemodynamic effects of opioids may vary depending on the opioid used, morphine causing a slight hemodynamic stimulation. However, all opioids studied could be considered hemodynamically stable.

4 INTRODUCTION

The term opioid was originally designated to drugs whose actions resemble morphine. This definition has been broadened to include morphine receptor agonists, as well as antagonists, that have a wide spectrum of action on the opioid system. Opioids are most commonly used for treatment of severe pain. Opioids exert their actions by binding to specific receptors in the central nervous system, the most important receptor type being the μ -receptor (Bailey et al 2000, Pugsley 2002, Waldhoer et al 2004). The most desired action of opioid receptor stimulation is analgesia. Also sedation and depression of cough reflex are usually considered beneficial opioid actions. A significant feature of opioid analgesia is that it is not associated with loss of consciousness. However, the fear of side effects has restricted the use of opioids, the biggest fear being respiratory depression. This has occasionally prevented the optimal use of opioids in treatment of pain. Respiratory depression caused by opioids has been extensively studied in patients, healthy volunteers and animal models (Jordan 1982, McClain et al 1984, Bailey et al 2000). A wide range of measurement methods have been used, ranging from simple respiratory rate measurement to sophisticated invasive monitoring, such as spirometers and pneumotachograms (Jordan 1982). Depending on the monitoring system used, different modes of respiratory effects have been noted in the previous studies.

Even though the administration of opioids is considered to provide hemodynamic stability, all opioids cause alterations to hemodynamics at least to some extent (Pugsley 2002). These effects have also been studied for decades and results have varied considerably, depending on the clinical situation (Kayaalp et al 1966, Zelis et al 1974, Flacke et al 1985, Bailey et al 2000, Carter et al 2002, Pugsley 2002). In the previous studies, the older opioids morphine and pethidine have been shown to cause more changes in hemodynamics than the newer ones, i.e., fentanyl and alfentanil. Some of these changes are thought to be mediated by histamine release (Bailey et al 2000).

In order to find a potent opioid analgesic with as little side effects as possible, different opioids have been compared with each other. Mostly, however, all opioids in equianalgesic doses produce the same degree of respiratory depression. (Bailey et al 2000). The incidence of other side effects may vary, however. The pharmacokinetic and pharmacodynamic profile of different opioids may vary greatly from short acting opioids like alfentanil to longer acting opioids, such as morphine and oxycodone.

The main goal of this series of investigations was to elucidate the native ventilatory and hemodynamic effects of different opioids. Also, the effects of ketamine, a non-opioid analgesic that produces little respiratory depression, was studied in conjunction with an opioid causing respiratory depression. Respiratory monitoring was chosen as non-invasive as possible in order to avoid the interference of monitoring with the actual drug effect on

ventilation. Unlike in many previous studies, opioids and ketamine were given to healthy volunteers and trauma patients as a sole medication and thus the effects found in these studies possibly represent a true opioid action.

5 REVIEW OF LITERATURE

5.1 Opioid receptors mediating respiratory depression

All opioids act in the central nervous system by binding to specific receptors, defined as opioid receptors (Table 1.) (Pugsley 2002, Fukuda 2005, Lalovic et al 2006). The activation of these receptors induce analgesia, ventilatory depression, sedation, euphoria, dysphoria, dizziness, depression of cough reflex, decreased gastrointestinal motility, nausea, vomiting and urinary retention. These effects are blocked by specific opioid receptor antagonists, such as naloxone.

Table 1. *Selectivity of opioids at the various opioid-receptor classes.*

	Receptor type			
Drug	μ	δ	κ	ORL-1
Morphine	+++	+	+	0
Oxycodone	++	+	+	0
Pethidine	++	+	+	0
Fentanyl	+++	+	+	0
Alfentanil	+++	+	+	0
Tramadol	++	+	+	0
Naloxone	---	-	--	0
Nociceptin	0	0	0	+
Ketamine	+	0	0	0

Agonist: + low, ++ moderate, +++ high affinity

Antagonist: - low, -- moderate, --- high affinity

0= no affinity ORL-1= orphan opioid receptor

There are three major groups of opioid receptors: mu (μ), kappa (κ) and delta (δ). These receptors have been further divided into subtypes: μ_1 , μ_2 , δ_1 , δ_2 , κ_1 , κ_2 , and κ_3 . An additional opioid receptor has been recently identified, the ORL-1 receptor (orphan opioid receptor). Its natural ligand is an endogenous peptide called nociceptin (Pugsley 2002). The μ -, δ - and κ - receptors mediate analgesia with considerable overlap. In the μ -receptor-family, analgesia is produced via μ_1 (supraspinal) and μ_2 (spinal)-receptors. Respiratory depression is mediated via μ_2 -receptor in brainstem, whereas μ_1 -receptor has been shown to induce respiratory stimulation (Bailey et al 2000, Pugsley 2002, Waldhoer 2004). Agonists selective

at δ -receptor have also a mild respiratory depressant effect, whereas κ -receptor agonists produce little, if not at all respiratory depression. Thus, respiratory depression is mainly mediated through μ_2 -receptor.

Sigma –receptor agonists stimulate ventilation; however, sigma-receptor is not classified as an opioid receptor, because sigma-receptor mediated effects are not reversed by opioid antagonists (Bailey et al 2000, Puglsey 2002, Waldhoer 2004).

The primary effect of opioid receptor activation is reduction of neurotransmission. All opioid receptors are linked through G proteins to inhibit adenylate cyclase. They also facilitate the opening of K^+ channels (causing hyperpolarization), and inhibit the opening of Ca^{+} channels (inhibiting transmitter release) (Pugsley 2002).

5.2 Respiratory effects of opioids

Respiratory depression induced by opioids is characterized by dose related, naloxone-reversible depression of resting minute ventilation (V_E), with decreased PaO_2 and increased $PaCO_2$. The diminution of V_E is mostly due to a slower rate of breathing (McClain et al 1984, Santiago et al 1985, Bailey et al 2000). Tidal volume (V_T) is either reduced or increased after opioid administration. The prolonged expiratory time (V_E) in the respiratory cycle induced by opioids frequently results in greater reductions in respiratory rate than in V_T (Drummond 1983). Opioids may also decrease the metabolic rate and the production of CO_2 , which results in lowered V_E (Jordan 1982, McClain et al 1984). The primary mechanism of respiratory depression induced by opioids involves a reduction in the responsiveness of the brainstem respiratory centers to CO_2 , evidenced as the decrease in the slope and rightward shift of the CO_2 response curve (McClain et al 1984, Bailey et al 2000). Also, the apneic threshold and resting end-tidal PCO_2 are increased by opioids. The peripheral chemoreceptor responsiveness to hypoxia is reduced with higher opioid doses. Opioids also blunt the increase in respiratory drive normally associated with increased loads, such as increased airway resistance (Bailey et al 2000). Another respiratory depressant mechanism reported with opioid administration is increased muscle rigidity, especially in conjunction with rapid administration of short acting opioids, such as fentanyl, alfentanil and remifentanil (Bailey et al 2000). In addition, postoperatively administered opioids may cause upper airway obstruction by loss of pharyngeal muscle tone (Bailey et al 2000). The respiratory depression induced by opioids is also potentiated by natural sleep (Jordan 1982).

5.2.1 Morphine

Most of the opioids in clinical use today are based on the structure of morphine. Morphine is a relatively selective μ -agonist, but will also interact with the other opioid receptors (δ , κ) at higher concentrations (Table 1). The pharmacokinetics of morphine is determined to a major degree by its low lipid solubility. After i.v. administration morphine is rapidly distributed, but its tissue penetration is slow due to this low lipid solubility. Slow brain penetration means that respiratory depression as well as analgesia are not necessarily reflected by plasma levels and may occur after a certain time lag, i.e., 10–15 minutes (Bailey et al 2000). However, a direct relationship between plasma morphine concentration and end-tidal CO_2 increase has also been reported (Hill et al 1990). Morphine is metabolized mainly to morphine-3-glucuronide (M3G) and less into morphine-6-glucuronide (M6G). M6G is a potent μ -receptor agonist with a weaker respiratory depressant action compared to morphine (Peat et al 1991, Thompson et al 1995).

The ventilatory effects of morphine have been studied both in patients and healthy volunteers. When 0.12–0.15 mg of morphine was given as an i.v. bolus to healthy volunteers breathing room air, it resulted in significant decrease in respiratory rate and V_E with an increase in PaCO_2 or end-tidal CO_2 (Rigg et al 1981, Peat et al 1991, Thomson et al 1995). The ventilatory response to CO_2 was also reduced together with mean inspiratory flow (V_T/T_I). V_T was not affected to the same degree as respiratory rate. When 10 mg of morphine was given to patients prior to anesthesia, similar effects were noted; decrease of respiratory rate, V_T and V_E . The decrease in respiratory rate and V_E persisted for up to 20–40 minutes, whereas the decrease in V_T was transient and later on changed to an enhancement of V_T (Orkin et al 1955). A decrease in respiratory rate and increase in V_T has also been reported in intensive care unit patients given 10 mg/70 kg of morphine. (Samuel et al 1977). Morphine administration of 10 mg/70 kg has been shown to decrease oxygen consumption (VO_2), measured with tidal pneumotachograph, when given to healthy volunteers breathing room air (Jennett et al 1968).

5.2.2 Oxycodone

Oxycodone resembles morphine in many respects, it is a synthetic derivative of thebaine and a selective μ -agonist (Brittain 1959, Lalovic et al 2006). It is metabolized to oxymorphone and noroxycodone, which are conjugated and excreted in urine. The equianalgesic dose ratio of oxycodone and morphine in earlier studies of postoperative patients varies from 1:1 (Brittain 1959, Silvasti et al 1998) to 2:3 (Kalso et al 1991). The clinical potency of oxycodone exceeds that of morphine, even though the μ -receptor binding affinity of oxycodone is lower than morphine. However, the blood-brain barrier penetration of oxycodone is higher than that of morphine (Lalovic et al 2006.) The lipid solubility of

oxycodone is suggested to be close to that of morphine (Pöyhiä et al 1994). However, the onset of analgesia and respiratory depression is faster with oxycodone than morphine. This might explain the deeper respiratory depression reported with oxycodone compared to morphine or pethidine (Takki et al 1973, Kalso et al 1991). In the postoperative phase 0.1 mg/kg oxycodone resulted in increase of end-tidal CO₂ by 0.6%, whereas 0.2 mg/kg increased end-tidal CO₂ by 1.0%, with a deeper dose-response curve than with pethidine (Takki et al 1973). Also in children, deeper respiratory depression after oxycodone than after other opioids has been reported (Olkola et al 1994). However, the more profound respiratory depression after oxycodone compared that after morphine has not been verified in all studies (Silvasti et al 1998).

5.2.3 Pethidine

Pethidine (meperidine) is a derivative of phenylpiperidine and a predominantly μ -receptor agonist; however, its μ -receptor binding affinity is slightly weaker than that of morphine. The potency of pethidine is approximately 1:7 to 1:10 compared to that of morphine. In equianalgesic doses, pethidine predominantly produces as much respiratory depression as does morphine. When given preoperatively to patients, 100 mg/70 kg intravenous pethidine decreases V_E and V_T , but increases the respiratory rate (Orkin et al 1955). In the postoperative phase, pethidine produces a slight (Muneyuki et al 1969, Welchew et al 1985) reduction or no effect at all (Keats et al 1968) on the respiratory rate, with a decrease in V_E and increase in PaCO₂. In children, the acute respiratory depression produced by pethidine is reported to be steeper but of shorter duration than that of morphine (Hamunen 1993). Subcutaneous infusion of 20 mg/h pethidine in the postoperative phase in adults does not seem to produce noticeable respiratory depression, when measured with respiratory rate (Davenport et al 1985). Pethidine is metabolized into norpethidine, which also has analgesic effects but is a potential convulsant (Bailey et al 2000).

5.2.4 Fentanyl

Fentanyl is a synthetic derivative of phenylpiperidine with faster onset and duration of action than pethidine. The analgesic onset time of intravenous fentanyl is about 1.5 minutes and the time to peak effect is 3.6–4.5 minutes. High lipid solubility and low plasma protein binding result in a large distribution volume (4.0 l/kg) (McClain et al 1980, Shafer et al 1991, Scholz et al 1996). The first pass uptake of fentanyl by lung tissue is up to 75% after an intravenous injection (Roerig et al 1987). The plasma fentanyl concentration decay is usually described by a three-compartment model, with plasma clearance of 10–20 ml/kg/min. T_{keo} of effect site concentration is 4.7–6.9 minutes (Scott et al 1985, Scott et al 1987, Ebling et al 1990). The mean effective analgesic plasma concentrations of fentanyl are approximately 1 and 3 ng/ml, respectively for postoperative and intraoperative administration. The CP₅₀ for

fentanyl at surgical skin incision with 70% N₂O is estimated to vary from 3.26 to 4.17 ng/ml (Glass et al 1993) and for experimental pain produced by dental pulp stimulation 1.3–1.8 ng/ml (Hill et al 1990). Ventilatory depression produced by fentanyl occurs at a CP₅₀ of 2.0–3.1 ng/ml, when measured postoperatively in surgical patients with CO₂ responsiveness (Cartwright et al 1983). After a single bolus administration on healthy volunteers, the EC₅₀ for respiratory depression is reported to be 4.6 ng/ml (Fung et al 1980). Adequate ventilation on recovery of anesthesia is possible when concentrations decrease to 1.5–2.9 ng/ml (Clotz et al 1991, Shafer et al 1991). Rapid bolus administration of fentanyl can be associated with muscle rigidity, especially when doses high enough to produce loss of consciousness are used (McClain et al 1984, White et al 1986, Neidhart et al 1989).

5.2.5 Alfentanil

Alfentanil is a synthetic derivative of phenylpiperidine. The high amount of non-ionized molecules of alfentanil at the physiological pH of 7.4 results in a very short onset time (0.75 min) and time to peak effect (1.4–1.5 min), because most of the drug can pass the blood-brain barrier (Shafer et al 1991, Scholz et al 1996). T_{Keo} of alfentanil's effect site concentration at the CNS is 0.9–1.1 min (Scott et al 1985, Scott et al 1987, Ebling et al 1990). Alfentanil is less lipid soluble than fentanyl, but more lipid soluble than morphine. The plasma clearance of alfentanil is less than that of fentanyl, approximately 6.4 ml/kg/min, and the steady state volume of distribution is 0.75–0.86 l/kg. Alfentanil is faster and shorter acting than fentanyl. The mean effective plasma concentration of alfentanil during surgery is between 250–350 ng/ml (Ausems et al 1986). The CP₅₀ of alfentanil for surgical skin incision associated with the use of 70% N₂O is 240 ng/ml and the alfentanil concentration required for recovery of spontaneous ventilation after general surgery varies between 125–226 ng/ml (Ausems et al 1986, Clotz et al 1991, Shafer et al 1991). The EC₅₀ of alfentanil for ventilatory depression during target controlled infusion in healthy volunteers is 49–60 ng/ml, when measured as V_E response to 7.5% CO₂. As well as with fentanyl, muscle rigidity produced by alfentanil is most often associated with bolus administration and is best treated with muscle relaxants (Benthuyssen et al 1986, White et al 1986). Muscle rigidity in conjunction with a high alfentanil bolus can be associated with decreased arterial oxygen tension (Benthuyssen et al 1986).

The relative potency of fentanyl and alfentanil at steady-state plasma concentrations has been verified mainly by three different methods. First, the ability of these drugs to reduce the MAC of isoflurane gives a potency ratio of 1:58 of alfentanil:fentanyl, respectively (Glass et al 1993, Westmoreland et al 1994). When using the slowing of EEG as a determinant of drug action, the relative potency of alfentanil and fentanyl varies between 1:66–1:70. (Ebling et al 1990, Gambus et al 1995, Scott et al 1985). The ability of these drugs to produce analgesia either during surgical procedure or during experimental pain condition, reveals the potency ratio of 1:40–1:58 (Hill et al 1990, Scott et al 1987). The potency ratio

for respiratory depression measured with steady-state plasma concentrations, however, has not been properly determined,.

5.2.6 Tramadol

Tramadol is a synthetic opioid of the aminocyclohexanol group. It is a moderately weak μ -agonist. It also enhances the function of the spinal descending inhibitory pathways by inhibition of reuptake of both norepinephrine and 5-hydroxytryptamine (5-HT) together with presynaptic stimulation of 5-HT release (Kayser et al 1992, Lee et al 1993, Desmeules et al 1996). The currently used tramadol is a racemic 1:1 mixture of (+)-tramadol and (-)-tramadol. The opioid receptor effects are mainly mediated by the (+)-enantiomer and the monoaminergic effects by (-)-enantiomer (Grond et al 1995). Tramadol is metabolized by the cytochrome P450 enzyme system in liver and the metabolite M1 of (+)-tramadol has higher affinity to μ -receptor than the parent compound itself. The potency of tramadol is often referred to be equianalgesic or slightly weaker compared to that of pethidine, when measured on mg to mg basis. When compared to morphine, the efficacy ratio is close to 10:1 (Vickers et al 1992, Lee et al 1993, Lehmann 1994). The respiratory effects produced by intravenous tramadol are often referred to be minimal when compared to other μ -agonists. This is probably due to moderately weak μ -receptor actions of tramadol. However, 1.0–1.5 mg/kg of intravenous tramadol has been shown to decrease the mouth occlusion pressure and minute volume response to CO₂ up to 25% (Seitz et al 1985). When comparing intravenous injections of tramadol 0.5, 1 and 2 mg/ml, a dose-response relationship was found only for respiratory rate, but not for end-tidal CO₂ or V_E (Vickers et al 1992). When comparing tramadol and pethidine during inhalation of 70% N₂O and 0.3% halothane, 0.6 mg/kg tramadol did not induce any respiratory depression, whereas 0.6 mg/kg pethidine caused a significant reduction in respiratory rate and minute volume (Tarkkila et al 1998).

5.3 Hemodynamic effects of opioids

In addition to pain relief, opioids are administered in order to suppress or block the hemodynamic stimulation induced by pain or surgery. However, in the absence of pain, opioids themselves may have some effects on hemodynamics, the most common of these being bradycardia. Opioid receptors are widely distributed in those regions of CNS which mediate various hemodynamic responses, i.e., nucleus solitarius, the dorsal vagal nucleus, the nucleus ambiguus and the parabrachial nucleus. The direct administration of μ -agonists into the CNS most commonly produces hypotension and bradycardia. Most opioids reduce sympathetic and enhance parasympathetic tone, which also predisposes a patient to bradycardia and hypotension. (Bailey et al 2000, Carter et al 2002). During anesthesia,

opioids also exert an antiarrhythmic action (Bailey et al 2000). The hemodynamic effects of opioids have widely been studied previously.

Table 2. *Hemodynamic effects of opioids*

Opioid	Source	Dose	Effect on HR	Effect on MAP	Other effects
Morphine	Kayaalp et al 1966	1–4 mg/kg (cats)	Increase	Increase	
	Lowenstein et al 1969	1 mg/kg	Decrease	0	No change in SVR
	Zelis et al 1974	15 mg	NDA	0	Venoconstriction
	Vatner et al 1975	2 mg/kg (dogs)	Increase	0	
	Rosow et al 1982	1 mg/kg	0	Decrease	Decrease in SVR
	Fahmy et al 1983	0.3 mg/kg	Increase	Decrease	Decrease in SVR
	Pfeiffer et al 1983	Enkephalin (rats)	Increase	Increase	
	Flacke et al 1985	0.6 mg/kg	0	Decrease	
	Muldoon et al 1987	3 mg/kg	Increase	Decrease	
	Warner et al 1991	1 mg/kg	NDA	0	No change in SVR
	Withington et al 1993	0.16 mg/kg	0	0	
	Doenicke et al 1995	0.15 mg/kg	0	0	
	Grossman et al 1996	Different doses	NDA	Increase	Venodilatation
	Carter et al 2002	0.075 mg/kg	Decrease	Increase	Increase in MSNA
Oxycodone	Takki et al 1973	0.1–0.2 mg/kg	0	0	
	Kalso et al 1991	21.8 ± 2.9 mg/kg	Decrease	Decrease	
	Pöyhiä et al 1992	0.28 mg/kg	Decrease	0	
Pethidine	Takki et al 1973	0.5–1.0 mg/kg	Increase	0	
	Flacke et al 1985	4.3 ± 0.2 mg/kg	Increase	Decrease	
	Bailey et al 2000	Different doses	Increase	NDA	Negative inotrope
Fentanyl	McClain et al 1980	3.2–6.4 µg/kg	Increase	Increase	
	Scott et al 1983	717 ± 414 µg	0	0	
	Neidhart et al 1989	21 µg/kg	NDA	Decrease	
	Bailey et al 2000	Different doses	0	0	
Alfentanil	McDonnel et al 1984	100–250 µg/kg	Increase	0	
	Benthuyssen et al 1986	175 µg/kg	Increase	Decrease	Muscle rigidity
	Ausems et al 1988	10 mg	Decrease	Decrease	
	Bailey et al 2000	Different doses	Decrease	0	
Tramadol	Chrubasik et al 1992	100–150 mg	0	NDA	
	Lee et al 1993	0.75–1.5 mg/kg	Increase	Increase	
	Radbruch et al 1996	Different doses	0	0	

NDA= no data available

SVR= systemic vascular resistance

MSNA=muscle sympathetic nerve activity

0 = no effect

5.3.1 Morphine

Morphine produces various hemodynamic changes, which are thought to be mediated by histamine release. The most frequent hemodynamic effect of morphine is the reduction of peripheral vascular resistance and baroreceptor reflex activity, resulting in peripheral vasodilatation and hypotension. These effects are most evident after large doses, or in patients with volume depletion, or in other forms of hypotension. Morphine 0.6 mg/kg induces tachycardia and hypotension when given during general anesthesia (Flacke et al 1985), whereas 0.15 mg/kg of morphine does not seem to have any effect at all on the hemodynamics of healthy volunteers (Doenicke et al 1995). Peripheral venodilatation induced by morphine is only partly antagonized by naloxone, which speaks in favor of non-opioid regulated vasodilatory mechanism (Grossman et al 1996). The vasodilatation induced by 15 mg intravenous morphine is possibly preceded by transient venoconstriction (Zelis et al 1974). A chronotropic effect of morphine can also be mediated by the release of catecholamines (Fahmy et al 1983, Muldoon et al 1987). In animal studies morphine has been shown to induce hypertension and tachycardia when given as a sole medication. However, when morphine administration was combined with β -blocking or anesthetic agents, this pressor reflex is changed to hypotension and tachycardia. (Kayaalp et al 1966, Vatner et al 1975, Pfeiffer et al 1983).

5.3.2 Oxycodone

The effects of oxycodone on hemodynamics are not widely studied. When given orally to healthy volunteers, 0.28 mg/kg of oxycodone decreased HR, but did not have any effect on MAP (Pöyhiä et al 1992). In the postoperative phase, a reduction of HR and blood pressure was achieved similarly after oxycodone and morphine administration (Kalso et al 1991). When compared to equianalgesic doses of pethidine and piritramide in the postoperative phase, hemodynamics remained more stable after oxycodone administration than after the others (Takki et al 1973).

5.3.3 Pethidine

When given i.v., pethidine commonly causes tachycardia. This may be related to its structural similarity to atropine or to the effect of norpethidine as an early manifestation of its toxic CNS effects. (Bailey et al 2000). Pethidine is reported to liberate histamine, even to a greater degree than morphine, which can also contribute to the chronotropic effect of pethidine. (Flacke et al 1987). Hypotension can result after pethidine administration. Pethidine itself is reported to have at least some degree of negative inotropic effects on myocardium (Bailey et al 2000).

5.3.4 Fentanyl

The effect of fentanyl on hemodynamics is minimal. It produces little or no change in most hemodynamic variables, i.e. HR, MAP, CO, even after large doses. (Bailey et al 2000). Plasma fentanyl concentrations adequate to produce slowing of EEG, i.e. 6.9 ng/ml do not affect hemodynamics (Scott et al 1985). The most frequent effect of fentanyl on hemodynamics is slight bradycardia, an effect of μ -agonists. However, in healthy subjects, 3.2 to 6.4 $\mu\text{g/kg}$ of fentanyl can cause increases in blood pressure and HR, which are preceded by hypercarbia (McClain et al 1980). A decrease in MAP has also been reported with 21 $\mu\text{g/kg}$ of fentanyl (Neidhart et al 1989).

5.3.5 Alfentanil

Alfentanil resembles fentanyl in the hemodynamic responses, which have been found to be minimal. Similarly to fentanyl, the plasma alfentanil concentrations adequate to produce slowing of EEG (520 ng/ml) and loss of consciousness (1012 ng/ml), preserve stable hemodynamics. However, there is evidence that alfentanil produces more hypotension and myocardial ischemia compared to fentanyl, when given during coronary surgery (Bailey et al 2000). An i.v. bolus of 10 mg alfentanil given at the induction of general anesthesia induced hemodynamic changes, hypotension and bradycardia, more often than a continuous, target controlled, computer-assisted i.v. infusion of the same dose (Ausems et al 1988). Muscle rigidity, which is often related to large intravenous bolus doses of alfentanil, is associated with decreases in MAP and increases in HR (Benthuisen et al 1986).

5.3.6 Tramadol

The effect of tramadol on hemodynamics is reported to be minimal, and no clinically relevant changes in heart rate or blood pressure were observed in the study of Radbruch et al (1996). On the other hand, Lee et al (1993) reported a slight and clinically insignificant increase in MAP and HR after 0.75 to 1.5 mg/kg intravenous doses of tramadol.

5.4. Histamine release by opioids

The opioids most frequently reported to release histamine are pethidine and morphine (Flacke et al 1987). The histamine-liberating action of morphine has been shown by Philbin et al (1981), who administered morphine in conjunction with both H_1 and H_2 -receptor blocking agents. They found a significant increase in plasma histamine concentration after

1 mg/kg of morphine. This was associated with a decrease in diastolic blood pressure and systemic vascular resistance. These hemodynamic effects were prevented by co-administration of both H₁- and H₂-blocking agents. This histamine liberating action of morphine has been confirmed by other authors as well (Rosow et al 1982, Moss et al 1983, Flacke et al 1987, Muldoon et al 1987, Withington et al 1993, Doenicke et al 1995). However, Warner et al (1991) have challenged these results by repeating the original study of Rosow et al (1982) with 1 mg/kg of morphine, and using more novel histamine assays, i.e. double-isotope radioenzymatic technique instead of single-isotope radioenzymatic assay as used by Rosow et al (1982). They found no increase in plasma histamine levels after morphine, as well as no change in hemodynamics (Warner et al 1991). However, the present opinion, which is mainly based on the studies by Rosow (1982), Flacke (1987), Muldoon (1987), Withington (1993) and Doenicke (1995), is that the clinically used doses of morphine cause a variable degree of histamine release.

The ability of oxycodone to liberate histamine appears to be minimal (Pöyhkä et al 1992, 2004). However, there may be considerable differences in species in this regard because oxycodone is reported to release histamine from porcine mast cells, even in higher amounts than morphine (Ennis et al 1991).

Histamine liberation of cutaneous mast cells produces local wheal and flare responses and possibly adverse hemodynamic effects (Hermens et al 1985, Levy et al 1989). These cutaneous wheal and flare responses after morphine and pethidine administration were similar to those after histamine and were not antagonized by naloxone. Unlike alfentanil, fentanyl is capable of producing wheal and flare responses, but these effects were antagonized by naloxone and were thought to be a result of a direct vasodilatory effect (Levy et al 1989). A rise in plasma histamine concentrations to 1.6 to 2.4 ng/ml seems to be needed for eliciting symptoms (Kalinier et al 1982). The clinical symptoms produced by these plasma concentrations are predominantly tachycardia and increase in pulse pressure.

5.5 Catecholamine release by opioids

While one of the rationales of opioid use is the prevention of stress responses, increases in catecholamine concentration has been shown after opioid administration. Fentanyl 0.1–0.25 mg/70 kg as well as morphine 10mg/70 kg given to healthy volunteers, resulted in dose-dependent increase in plasma norepinephrine concentrations, whereas plasma epinephrine levels were increased only with lower fentanyl doses (Hoeche et al 1993). This action of opioids is thought to be mediated by μ - as well as κ -receptors. Both morphine and pethidine administration can be accompanied by catecholamine release (Taborsky et al 1981, Fahmy et al 1983, Flacke et al 1985, Muldoon et al 1987). This release of epinephrine is also thought to be secondary to histamine release (Fahmy et al 1983, Muldoon et al 1987).

5.6 Other opioids

Other opioids from the phenylpiperidine group that are frequently used are sufentanil and remifentanil. Sufentanil resembles fentanyl, with similar T_{keo} of effect site, i.e., 6.5 min (Fukuda 2005, Lötsh 2005a). However, sufentanil has a 12-fold greater potency than fentanyl shifting the EEG spectral edge to the left. Remifentanil is a very short-acting opioid, with a high plasma clearance by de-esterification via blood esterases. Also, the steady-state distribution volume of remifentanil is small. T_{keo} of effect site for remifentanil resembles that of alfentanil, i.e., 1.6 min. (Fukuda 2005, Lötsh 2005a), but remifentanil is 19 times more potent than alfentanil in slowing down EEG. Despite its unique pharmacokinetic profile, the pharmacodynamic effects of remifentanil parallel those of fentanyl and alfentanil. (Beers et al 2004). Also, no histamine release is documented after remifentanil administration. (Fukuda 2005). 50% reduction in isoflurane MAC may be achieved at remifentanil whole blood concentration of 1.37 ng/ml.

Opioids that are often compared to tramadol in analgesic potency are codeine and buprenorphine. Both are so called weak opioids and have a plateau in dose-response curve. Buprenorphine is a semisynthetic derivative of thebaine and is a partial μ -opioid receptor agonist and κ -receptor antagonist with a long duration of action (Boothby 2007). The opioid antagonist effects observed with buprenorphine treatment are similar to those observed with naloxone. The pharmacokinetic and pharmacodynamic profiles of buprenorphine are not well characterized; however, the respiratory depressant effects of buprenorphine are similar to those of morphine when equipotent doses are used (Boothby 2007). Codeine is a weak μ -receptor agonist and is metabolized via CYP₄₅₀2D6 by 10% into morphine. Codeine analgesia depends on this metabolism. (Lötsh 2005b).

5.7 Ketamine

Ketamine is a non-opioid drug, which acts as an antagonist of N-methyl-D-aspartate (NMDA) –receptors in the CNS. Ketamine also possesses some activity towards non-NMDA glutamate receptors, opioid receptors, monoaminergic receptors and cholinergic receptors. However, the clinical significance of these actions is not clear (Hirota et al 1996). Commercial Ketamine is available as a pure S (+)-enantiomer and as a 1:1 racemic mixture of S (+)-ketamine and R (-)-ketamine. S (+)-ketamine has been shown to be three times more potent than R (-)-ketamine. Ketamine has a relatively short distribution half-life of 24 seconds and elimination half-life of $t_{1/2\alpha}$ 5–17 minutes and $t_{1/2\beta}$ 137–180 minutes (Clements et al 1981, Reich et al 1989). Ketamine is metabolized by the liver, the most important pathway being N-demethylation by CYP₄₅₀ to norketamine, an active metabolite with an anesthetic potency one third of that of ketamine (Reich et al 1989).

Ketamine induces a dose-dependent depression of CNS that leads to a so-called dissociative state, characterized by profound analgesia and amnesia but not necessarily loss of consciousness. Racemic ketamine produces anesthesia with doses of 1–2 mg/kg, but analgesia can be achieved with smaller doses, i.e. 0.25–0.5 mg/kg (Clements et al 1981, Kohrs et al 1998). In contrast to other anesthetic agents, the use of ketamine is favored by its minimal effects on respiration and its ability to stimulate hemodynamics. Ketamine is reported either to stimulate (Soliman et al 1975, Roytblat et al 1986, Morel et al 1986), depress or have no effect at all on respiration; however, all these effects are considered clinically minimal (Corssen et al 1966, White 1982). Ketamine also acts as a bronchodilator and it generally preserves airway patency, which both contribute to preserved respiratory function. Ketamine has negative inotropic actions on the myocardium, but it has a centrally mediated ability of catecholamine release, which results in an increasing HR, blood pressure and CO (Traber et al 1968). Whole body and myocardial VO_2 is increased after ketamine administration, most probably due to the increased sympathetic tone (Tweed et al 1972, Taittonen et al 1998).

The use of ketamine as a sole agent is limited by its unpleasant psychotomimetic actions: hallucinations and vivid dreams. Therefore, ketamine is often combined with other sedatives or analgesics in order to counteract both psychomotor and cardiovascular effects. Ketamine has been combined with benzodiazepines like midazolam (Taittonen et al 1998), anesthetics like propofol (Hui et al 1995), α_2 -agonists like clonidine and dexmedetomidine (Levänen et al 1995, Taittonen et al 1998) and opioids like morphine (Bourke et al 1987, Edwards et al 1993).

5.8 Effect of pain on breathing and hemodynamics

Both injury-related and experimental pain can change breathing pattern and induce various changes in ventilatory dynamics. In general, pain, including surgery, is reported to antagonize the respiratory depression induced by opioids. In experimental studies, pain stimulation can be achieved by different methods. In the cold pressor pain test the upper arm is immersed in ice water for a certain period of time. In the dental stimulation pain test, an electrical current is conducted to a tooth with a predetermined current. In tourniquet pain testing, both upper and lower extremities can be used for keeping a tourniquet inflated for a certain period of time (Hagenouw et al 1986). The upper arm tourniquet technique can be further extended by the subject squeezing a hand exerciser during the tourniquet inflation (Smith et al 1966). In a study of Borgbjerg et al (1996) and Nishino et al (1999), the tourniquet inflation increased V_T , V_E and the mouth occlusion pressure response to CO_2 . The tourniquet technique produced an increase in blood pressure, whereas the HR remained at the baseline level (Hagenouw et al 1986).

5.9 Effect of oxygen on breathing

Oxygen is frequently administered in conjunction with opioids in order to prevent hypoxia due to ventilatory depression (Bailey et al 2000). However, the effect of supplemental oxygen on ventilatory function is not necessarily beneficial. The use of hyperoxygenation during the induction of anesthesia produces more atelectasis than lower oxygen concentrations. This atelectasis formation is associated with low lung volumes, i.e. volumes close to residual volumes. Even the use of 30% supplemental oxygen is associated with increased atelectasis formation (Nunn et al 1978, Rothen et al 1995, Reber et al 1996). The formation of atelectasis correlates with the formation of shunt and arterial desaturation (Reber et al 1996).

Administration of oxygen to healthy volunteers during constant end-tidal CO_2 stimulates ventilation by increasing V_E in dose dependent fashion. After 30 minutes of 75% O_2 , V_E is more than doubled and even after 30% O_2 , V_E is increased 20%. The increase in V_E is mainly due to increase in V_T ; however, respiratory rate was also increased with higher oxygen concentrations. If normocapnia is not maintained, hyperventilation is attenuated by a decrease in PaCO_2 . The reason for this phenomenon is thought to be a result of the Haldane effect, in which noroxygenated hemoglobin has a higher transport capacity for CO_2 than does oxygenated hemoglobin because of the reduced carbamino carriage and the decreased buffering capacity of oxygenated blood (Becker 1995, 1996).

5.10 Respiratory measurements

The effects of opioids on the regulation of breathing may be studied by analyzing the breathing pattern and gas exchange in undisturbed subjects at rest or by analyzing the response of ventilation to challenges, such as increased CO_2 or decreased O_2 tension (McClain et al 1984).

5.10.1 Measurements of resting ventilation

5.10.1.1 Analysis of breathing pattern

The breathing movement can be regarded as a mechanical event in the respiratory control mechanism. Traditionally, breathing pattern has been analyzed solely as tidal volume (V_T) and frequency (Fr), which are the determinants of minute volume (V_E). The respiratory cycle can further be described by the duration of inspiration (T_I), duration of expiration (T_E) and total cycle duration (T_{TOT}). V_E can be splitted into driving and timing components as follows:

$$V_E = f \times V_T = 1/T_{TOT} \times V_T/T_I \times T_I = V_T/T_I \times T_I/T_{TOT}$$

V_T/T_I is an index of the intensity of respiratory drive and T_I/T_{TOT} represents timing of the respiratory cycle. The relationship of V_T/T_I to airway occlusion pressure ($P_{0.1}$), a classical index of respiratory drive, is well established (Milic-Emili 1982, Tobin et al 1983, McClain et al 1984).

5.10.1.2 Pneumotachometry

In the intubated patient, ventilation can be easily measured by attaching a spirometer or pneumotachograph to the patient's endotracheal tube. With spirometer the change in spirometer volume is being recorded and with pneumotachometer the pressure difference across the pneumotachometer head is proportional to flow, which is then integrated to volume signal. (Jordan 1982). In non-intubated patients, these methods necessitate the use of tight-fitting face masks or mouthpieces, which can produce spurious alterations in breathing pattern, causing V_T to increase and respiratory frequency to decrease with unpredictable changes in V_E and increases in V_T/T_I (Gilbert et al 1972, Jordan 1982, Weissman et al 1984, Han et al 1997). The use of a face-mask can also add dead space and resistance to breathing. However, the use of a spirometer enables the measurement of $P_{0.1}$, a characteristic of respiratory drive (Jordan 1982, McClain et al 1984).

5.10.1.3 Airway occlusion pressure

$P_{0.1}$ can be obtained by performing inspiratory occlusions without warning at irregular intervals and by measuring the change in airway pressure at 0.1 seconds after starting the occlusion. $P_{0.1}$ is used as an index of respiratory center motor output and correlates well with the diaphragmatic electromyogram and increases linearly with CO_2 tension (Jordan 1982, McClain et al 1984).

5.10.1.4 Respiratory inductive plethysmography

Respiratory inductive plethysmography (RIP) is a device developed for quantitative and noninvasive measurements of resting ventilation. RIP is based on the magnetometry principle established by Konno and Mead (1967). They found that movements and volume changes of the respiratory system can be approximated to two degrees of freedom of motion. At any given moment the total change in the volume of the respiratory system will correspond to the sum of the volume changes in the thoracic and abdominal compartments. The respiratory movements of the rib cage and abdominal compartments can be measured by external sensors, i.e., magnetometers as originally described by Konno et al 1967 or inductive plethysmograph (Milledge et al 1977), and calibrated to yield quantitative data (Sackner et al 1989). The RIP represents a modern application of the Konno-Mead

principle. It provides a good accuracy of volume measurement over a wide range of body positions (Jordan 1982, Watson et al 1988, Valta et al 1992).

5.10.2 Ventilatory challenges

Respiratory center output is typically measured with ventilatory challenges. Ventilation can be challenged either by hypercapnia or hypoxia. The response of ventilation to an increase in CO_2 is considered a particularly sensitive test of respiratory depression (McClain et al 1984). Increases in PaCO_2 stimulate the peripheral arterial chemoreceptors directly and the central chemoreceptors in the brain indirectly through concomitant changes in brain extracellular pH. The respiratory centers of pons and medulla respond to the information from the chemoreceptors and increase ventilation in order to keep PaCO_2 constant (Jordan 1982). In the hypercapnic ventilatory challenge, the fraction of inhaled CO_2 is increased either stepwise as in the steady-state method or more commonly linearly with the rebreathing method (Read et al 1967). V_E is then measured together with PaCO_2 and plotted on a linear curve. There is a wide variability in the slope of the ventilatory response to CO_2 between individuals. The day-to-day variability within individuals is also large. Ventilatory challenges can also induce changes in hemodynamics. The steady-state method produces clear increases in blood pressure, heart rate and decrease in total peripheral resistance (Cullen et al 1974).

Hypoxia stimulates ventilation primarily through its action on carotid body chemoreceptors. The ventilatory response to change in oxygen tension is very rapid and might even be more sensitive than the response to increased CO_2 (McClain et al 1984). In the hypoxic ventilatory challenge (hypoxic roll-off) the inspired oxygen fraction is continuously or stepwise decreased and sustained for 20 minutes and V_E measured at certain PaO_2 levels.

5.10.3 Measurements of gas exchange

5.10.3.1 Indirect calorimetry

Originally, the rate of whole-body VO_2 is based on an application of Fick's equation: $\text{VO}_2 = \text{CO} \times \text{AVDO}_2$, where AVDO_2 is the difference in arterial and mixed venous blood O_2 content. However, the use of the Fick's equation requires the use of pulmonary artery catheterization and it gives only a single measurement of VO_2 . Furthermore, it does not measure whole body VO_2 , because it excludes lung parenchymal VO_2 .

Indirect calorimeters are devices designed to measure VO_2 and VCO_2 in order to calculate metabolic rate. They are divided into open-circuit and closed-circuit categories. The open-circuit system is analogous to the so-called Douglas bag method, where the determinants of

VO_2 and VCO_2 are the differences between inspired and expired O_2 and CO_2 concentrations, and expired V_E (Meriläinen 1987, 2000).

Using a specially designed canopy, these measurements can be performed in non-intubated spontaneously breathing patients. As no mouthpiece is needed, indirect calorimetry does not cause changes in breathing pattern or lung volumes. The sensitivity and accuracy of O_2 and CO_2 sensors make rapid and precise analysis of VO_2 and VCO_2 possible. This has expanded their use from metabolic rate studies to ventilatory measurements.

5.10.3.2 Blood gas analysis

Measurements of arterial blood-gas tensions are the mainstay of the clinical assessment of ventilation, although the information obtained has its limitations (McClain et al 1984). Arterial blood sampling and subsequent blood-gas analysis enable PaO_2 , PaCO_2 to be measured directly. Adequacy of ventilation may be assessed from measurements of arterial PCO_2 , an increase in PaCO_2 implying that V_A has diminished in relation to VCO_2 . Measurements of PaO_2 are generally considered less useful in measurements of ventilatory function, since it is dependent on the relative distribution of pulmonary ventilation and perfusion (Jordan 1982).

5.10.3.3 Alveolar ventilation

V_A is referred as the portion of V_E that respire, i.e. removes CO_2 from the blood and transfers O_2 through the lungs to the blood. The portion of V_E that does not respire is designated as dead space ventilation (V_D). The rate of carbon dioxide production (VCO_2), obtained from indirect calorimetry, and the alveolar partial pressure of carbon dioxide (PACO_2) thus determine the need for alveolar ventilation (Kiiski et al 1991, Tulla et al 1995.) PaCO_2 is a function of PACO_2 . The correlation between metabolism and breathing can be expressed mathematically by the Bohr equation: $V_E = k \times \text{VCO}_2 / \text{PaCO}_2 \times (1 - V_D/V_T)$, with $k=0.115$ in spontaneously breathing patients and $k=0.863$ in intubated patients. V_A is further determined by $V_A = V_E \times (1 - V_D/V_T)$ (Kiiski et al 1994).

6 AIMS OF THE STUDY

The aim of the study was to clarify the effects of different opioids and ketamine on respiration and hemodynamics in healthy volunteers and trauma patients. Respiratory depression, evaluated as changes in breathing pattern, gas exchange and blood gas values, was the main parameter in this study.

The specific aims of this study were

- To evaluate the native respiratory effects of i.v. morphine (III), oxycodone (III, V), pethidine (II), tramadol (II), fentanyl (I and IV) and alfentanil (IV).
- To calculate the potency ratio for respiratory depression of fentanyl and alfentanil at steady-state plasma concentrations (IV).
- To evaluate whether ketamine could attenuate fentanyl-induced respiratory depression (I).
- To investigate the immediate cardiovascular responses to i.v. morphine and oxycodone under experimental pain (III) and the cardiovascular responses to i.v. fentanyl- (IV), alfentanil- (IV), pethidine- (II) and tramadol- (II) infusions.
- To investigate the effects of opioids on plasma catecholamine and histamine concentrations during experimental pain (II,III)
- To evaluate the effect of supplemental oxygen on respiration and atelectasis formation on trauma patients treated with oxycodone (V)

7 SUBJECTS AND METHODS

7.1 Volunteers and patients

Studies I–IV were carried out at Turku University. These studies each involved 8 healthy male volunteers, age 22–35 years. All volunteers were interviewed and clinically examined before participation. Before study IV a drug-screening test was also performed. No alcohol or drug abuse, allergy, permanent medication, smoking >10 cigarettes/day were allowed for any of the subjects. Study V was carried out in the emergency department of the trauma center of Helsinki University Hospital, Töölö Hospital during November 1997–May 1998. This study involved 13 patients, 8 male and 5 female with mean age 15–58 years. Patients with lower or upper extremity injury without any injury to head, thorax or abdomen were included in the study. The participants were recruited right after arrival to the emergency room.

7.2 Ethical aspects

The studies were conducted in accordance with the guidelines of the declaration of the World Medical Assembly of Helsinki. The study protocols of studies I–IV were approved by the Joint Commission on Ethics of the Turku University and the Turku University Hospital, and study IV was also approved by the Finnish National Agency for Medicines. The study protocol of study V was approved by the Ethics Committee of Töölö Hospital in Helsinki University Hospital. Before participating, all volunteers and patients were informed about the purpose and nature of the study. A written informed consent was obtained from each volunteer and patient.

7.3 Study design

The summary of the study designs is presented in Table 3. Also, the general setting of studies I–IV is depicted in Figure 1.

Table 3. *Summary of the study designs*

Study number	Number of volunteers/ patients	Design	Drugs, doses, timing	Key parameters
I	8 volunteers	Double-blind, randomized, cross-over, placebo-controlled	Fentanyl 2µg/kg+ Ketamine 0.25 mg/kg or Fentanyl 2µg/kg+placebo	V_E , V_A , VO_2 , SpO_2 , MAP, HR
II	8 volunteers	Double-blind, randomized, cross-over, controlled	Tramadol 150 mg bolus + 250 mg 3 h infusion or Pethidine 112.5 mg bolus + 187.5 mg 3 h infusion	SpO_2 , V_D , RR, V_T/T_I Plasma catecholamines
III	8 volunteers	Double-blind, randomized, cross-over, placebo-controlled	Morphine 0.07 mg/kg or Morphine 0.14 mg/kg or Oxycodone 0.14 mg/kg or placebo	MAP, HR, VO_2 , Plasma histamine and catecholamines, V_A
IV	8 volunteers	Double-blind, randomized, cross-over, controlled	Alfentanil as 5,8,12.5,20,31.5, 50,80,125,200,315,500 ng/ml concentrations and Fentanyl as 0.1,0.16,0.25,0.4, 0.63,1.0,1.6,2.5,4.0,6.3, 10 ng/ml concentrations	Pharmacodynamic modeling, V_E , RR, $PaCO_2$, V_A
V	13 trauma patients	Randomized, controlled	Oxycodone 0.08 mg/kg (+ additional 0.04 mg/ml if requested) for all patients 40% oxygen or room air	Atelectasis formation, PaO_2 , SpO_2

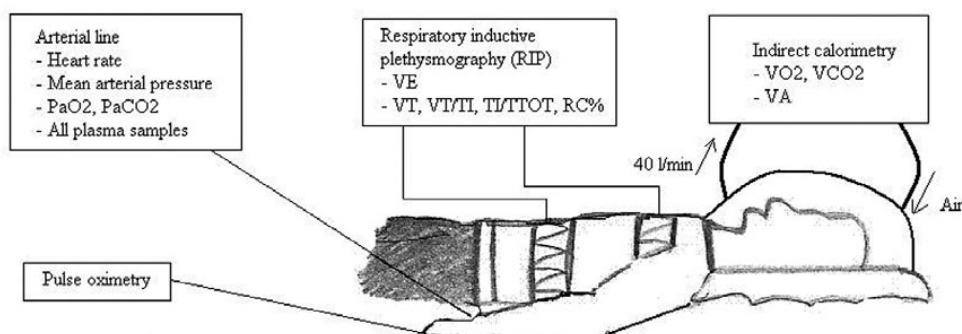


Figure 1. *The general setting of studies I-IV.*

Study I. The effect of low-dose ketamine 0.25 mg/kg on the respiratory depression induced by fentanyl 2 µg/kg was studied in eight healthy volunteers. The effects of fentanyl+ketamine and fentanyl+placebo on V_E, V_A, V_O₂, PaO₂, SpO₂, MAP and HR were measured during a 60-minute follow-up period. The study was performed in randomized, placebo-controlled, double-blind and cross-over fashion.

Study II. Tramadol 150 mg i.v. bolus followed by 250 mg as 3 hour steady i.v. infusion were compared to those of pethidine 112.5 mg IV bolus followed by 187.5 mg as 3 hour steady i.v. infusion during experimental pain stimulus. Breathing pattern, PaCO₂, SpO₂, MAP, HR and plasma catecholamines were measured in eight healthy volunteers, studied in randomized, cross-over and double-blind fashion. All measurements were performed until 60 minutes after cessation of the infusion.

Study III. The initial effects of single i.v. dose of morphine 0.07 mg/kg, 0.14 mg/kg and oxycodone 0.14 mg/kg during first 30 minutes on MAP, HR, V_O₂, V_A, PaO₂ and plasma catecholamines and histamine were studied in eight healthy volunteers in randomized, cross-over, double-blind and placebo-controlled fashion. Experimental pain stimulus was used during the study.

Study IV. The potency ratio for respiratory depression of alfentanil and fentanyl was studied during logarithmically escalating plasma pseudo-steady-state alfentanil and fentanyl concentrations. The drugs were delivered with a computer controlled infusion pump and the infusions were terminated when respiratory rate decreased to 2/min or SpO₂ decreased below 85%. During the infusions, V_E, V_A, breathing pattern, V_O₂, V_{CO}₂, PaO₂, PCO₂, MAP, HR as well as plasma alfentanil and fentanyl concentrations were measured. Pharmacodynamic modeling was performed in order to calculate EC₅₀ values for V_E and respiratory rate as well as a linear model in the increase in PaCO₂. The study was performed in eight healthy volunteers in randomized, double-blind, cross-over fashion.

Study V. The effect of supplemental oxygen on respiration of opioid-treated trauma patients was studied in randomized and controlled fashion in 13 patients. Patients with upper or lower extremity trauma were given i.v. oxycodone 0.08 mg/kg and randomized to either breathe 40% oxygen via facemask or room air. Additional oxycodone 0.04 mg/kg i.v. was given, if so requested by the patient. SpO₂, PaO₂, PaCO₂, MAP and HR monitored starting 5 minutes before and continued up to 30 minutes after first oxycodone administration. After 30 to 60 minutes a computer tomography of the chest was performed in order to evaluate atelectasis formation.

7.4 General considerations

The general study setting used in studies I–IV is presented in Figure 1. During studies I–IV no food, caffeinated drinks or chocolate were allowed up until 12 hours before the study session. No alcohol was allowed on the preceding day of the studies. To exclude diurnal variation, both sessions for each subject were performed at the same time of the day. During the experiments the subjects were breathing room air and were resting supine in bed in a normally lighted room with ambient room temperature. The double-blind nature of the studies was ensured by having an independent person not participating in the actual study prepare the study drugs into ready-to-inject form. Physiologic saline was used as placebo in studies I and III. No glucose was infused during the study periods of studies I–IV. The washout period between study session in studies I–IV varied from 5 days to 3 weeks. During study V the patients lay in hospital beds and were instructed to lie quietly unless they had any complaints. Ringer's acetate was infused during study V for all patients, approximately 50–100 ml/h.

7.5 Study drugs

The following drugs were used during the study: morphine (Morfin®, Leiras, Turku, Finland), oxycodone (Oxanest®, Leiras, Turku, Finland), pethidine (Petidin®, Leiras, Turku, Finland), tramadol (Tramal®, Orion-Farmos, Espoo, Finland), fentanyl (Fentanyl®, Orion-Farmos, Espoo, Finland), alfentanil (Rapifen®, Orion-Farmos, Espoo, Finland), ketamine (Ketalar®, Parke-Davis, Detroit, USA).

7.6 Measurements

7.6.1 Respiratory monitoring

7.6.1.1 Respiratory inductive plethysmography

The respiratory inductive plethysmograph (RIP, Resptrace TM, NIMS, Miami Beach, FL, USA) was used in studies I, II, IV for measurement of breathing pattern, in addition to this in studies I and IV for measurement of minute ventilation. In studies III and V RIP was used for measurement of respiratory rate and as an apnea monitor. Changes in rib cage (RC) and abdominal circumferences (AB) were simultaneously measured using two differential linear transformers connected to tight fitting belts around the chest at nipple level and around the abdomen at umbilical level. As the respiratory movements change the cross-sectional areas of the rib cage and the abdominal compartments, the self-inductance of insulated wire coils worn around the rib cage and the abdomen changes in proportion to the change of the cross-sectional area during tidal breathing. The respiratory movements produce variation in the self-inductance of the transducer. The signal obtained from this is demodulated to produce analog waveforms of RC and AB excursions and the sum signal. The sum signal can be calibrated against a volume reference to provide volumetric measurements (Sackner et al 1989).

In the beginning of studies I and IV, the RIP was calibrated using the semi-quantitative single-position calibration method designed by Sackner et al (1989). Baseline breathing was first collected for five minutes and thereafter calibrated against a calibrated heated pneumotachometer (PT) (Hans Rudolph Inc, Kansas City, MO, USA), connected to a differential pressure transducer (Validyne MP 45, ± 2.0 cmH₂O; Validyne Co, Northridge, CA, USA). Flow, volume and analog RC+AB signals were amplified and recorded using a physiologic recording system (Direc, Raytech Instruments, Vancouver, Canada). The calibration of RIP was completed by comparing the V_T determined by the RIP against those determined by the PT. At least five breaths were sampled for calibration. The calibrated sum signal was analyzed with a software program (Respievents, NIMS) provided with the RIP. The calibration was validated and accepted only if the measured error of the sample of breaths was within the range of $\pm 5\%$. For each measuring point breathing pattern or respiratory rate was measured for 2 minutes. V_E was calculated from V_T and respiratory rate. V_T/T_I was calculated dividing V_T with T_I . Also, the proportion of total ventilation that can be attributed to expansion of rib cage (RC%) was measured.

In the beginning of studies II, III and V no volumetric calibration was performed. Otherwise the design was similar to studies I and IV.

7.6.1.2 Arterial blood gas analysis

Arterial blood from a cannula inserted in the radial artery was drawn for analysis of PO₂ and PCO₂ in all of the studies. The blood samples were chilled on ice and analyzed within 20 minutes.

7.6.1.3 Arterial hemoglobin oxygen saturation

SpO₂ was recorded in all studies using a pulse oximeter (Cardiicap, Datex-Ohmeda, Helsinki, Finland) with a finger probe.

7.6.1.4 Alveolar ventilation

V_A was calculated according to formula $V_A = 0.115 \times VCO_2 (\text{ml/min}) / PaCO_2 (\text{kPa})$ (Kiiski et al 1994, Tulla et al 1995).

7.6.2 Hemodynamic measurements

In all studies MAP and HR were directly recorded from the radial artery (Cardiicap, Datex-Ohmeda, Helsinki, Finland). In studies II, IV and V continuous monitoring of ECG was also performed (Cardiicap, Datex-Ohmeda, Helsinki, Finland). Collect-program (Datex-Ohmeda, Helsinki, Finland) was used for the collection of hemodynamic and metabolic data in all the studies.

7.6.3 Measurements of gas exchange

The gas exchange measurements in studies I, III and IV were performed using an open-system indirect calorimeter Deltatrac® (Takala et al 1989).

For the measurement of spontaneously breathing patients, the subjects head is placed under a plastic canopy connected to the analyzer (Meriläinen 1987). The difference between FiO₂ (measured at the entry valve of the canopy) and FeO₂ is measured with fast-response paramagnetic differential O₂ sensor (OM-101, Datex/Instrumentarium, Helsinki, Finland). The FeCO₂ is measured with an infrared CO₂ sensor.

VCO₂ is calculated as the product of the constant flow and the fraction of CO₂ in the diluted expiratory flow: $VCO_2 = Q \times 1/FeCO_2$, where Q is the constant flow. The VO₂ is calculated using the Haldane transformation: $VO_2 = VCO_2/RQ$, where $VCO_2 = Q \times 1/FeCO_2$ and $RQ = 1 - FiO_2 / ((FiO_2 - 1/FeO_2) / FeCO_2 - FiO_2)$. FeO₂ and FeCO₂ are the fraction of O₂ and CO₂ in the mixed expiratory gas flowing through the monitor (Meriläinen 1987). The

Deltatrac monitor was calibrated with a gas mixture of $5.0 \pm 0.03\%$ CO₂ and $95 \pm 0.03\%$ O₂ (Calibration Gas, Datex).

7.6.4 Biochemical determinations

Arterial blood samples were drawn from the radial artery for measurements of plasma epinephrine and norepinephrine (II,III), histamine (III) and alfentanil and fentanyl (IV) concentrations. The blood samples were collected in pre-cooled EDTA-tubes, chilled on ice, and promptly centrifuged at 4°C. Plasma was stored at -70°C until analysis.

Plasma concentrations of catecholamines were determined using high-performance liquid chromatography (HPLC) with electrochemical detection (Scheinin et al 1991). The intra-assay coefficients of variation were <2% for norepinephrine and 10% for epinephrine. Plasma concentrations of prolactin were determined using a commercially available radioimmunoassay (RIA, Orion Diagnostica, Espoo, Finland). Plasma concentrations of histamine were determined with high-performance liquid chromatography by using a cation exchange column with postcolumn derivatization and fluorescence detection (Yamatodani 1985, 1991). Plasma levels of alfentanil and fentanyl were determined using radioimmunoassay methods (Michiels et al 1983, Woestenborgh et al 1987).

7.6.5 Computer controlled infusions

In study IV alfentanil and fentanyl were delivered with a computer driven (STANPUMP) infusion pump (Harward 22 Basic Syringe Pump, Harward Apparatus, South Natick, MA, USA) based on a pharmacokinetic model. (Scott et al 1987, Shafer et al 1991). Ascending logarithmic escalations of pseudo steady-state plasma drug concentrations were accomplished at 10 minutes intervals.

7.6.6 Pharmacodynamic modeling

In study IV pharmacodynamic modeling was performed separately for each subject using the nonlinear regression program PCNONLIN (Version 4.2, Scientific Consulting Inc., Apex, NC, USA) without weighting. The concentrations producing 50% of the maximal decrease in V_E and respiratory rate (i.e. apparent EC₅₀ values) were estimated by fitting the fractional E_{max} and sigmoidal E_{max} models to the data according to equations 1 and 2, respectively,

$$E = E_0 \times [1 - C / (EC_{50} + C)] \quad (1)$$

$$E = E_0 \times [1 - C^\gamma / (EC_{50}^\gamma + C^\gamma)] \quad (2)$$

where E is effect, E_0 is baseline effect (maximal drug effect, E_{\max} is equal to E_0), C is drug concentration, EC_{50} is concentration at 50% of E_{\max} and γ is sigmoidicity (Hill) factor. (Bouillon et al 1999). The goodness of the fits was determined by Akaike's information criterion and by assessment of scatter of the observed data points in relation to the fitted function. In addition, the increase in PaCO_2 was fitted to a linear model, i.e.

$$E = E_0 + k \times C \quad (3)$$

where k is the slope of the line relating effect to concentration.

7.6.7 Pain assessment

Pain stimulus was used in studies II and III. Experimental pain was induced using a 7-cm wide upper arm tourniquet inflated to 300 mmHg for 5 (II) or 10 (III) minutes as described by Hagenouw et al (1986). In study II pain stimulus was used at baseline, after the bolus dose of study drugs and at the end of drug infusion. In study III pain stimulus was started prior to drug injection and lasted up to 4 minutes after drug injection.

7.6.8 Subjective assessments

VAS-scales with subject marking on a 10-cm long ungraded horizontal line with opposite extremes at each end were used to obtain subjective estimates on the experience of pain (II), nausea (II,III), euphoria and dysphoria (I,III), dizziness, dryness of mouth and sedation (I) (Maxwell 1987).

7.6.9 Radiological assessment

In study V, 12 of 13 patients recruited in the study went through a CT scan of chest for evaluation of atelectasis. No CT-scan was performed on one patient because of technical problems. For the CT scan (GE HiSpeed) the subjects were supine with their arms above the head. A spiral CT of the lungs was performed at the end of inspiration, the slice thickness being 1 mm with 10 mm intervals (erratum in the Study V). No contrast medium was used. All CT images were evaluated and atelectasis or other signs of hypoventilation were recorded as "yes" or "no". Two CT scans from each patient were chosen for further analysis. The chosen scans were 6 cm (upper) and 2cm (lower) above the diaphragm. A region of interest (ROI) was drawn in both lungs separately. This region excluded the outermost part of the lung to avoid partial volume effect. Also, the great vessels were excluded medially. A histogram of the distribution of pixel density was made in these ROI areas and lung

density was defined in terms of Hounsfield units (Lundquist et al 1995). A value above 500 Hounsfield units was considered a poorly aerated lung. The calculations were carried out both on the right and left lung separately.

7.6.10 Statistics

In studies I,II and III statistical analysis was performed using Statview SE Graf software for Macintosh (Abacus Concepts, Berkely, CA, USA). Students unpaired t-test was used for statistical analysis for comparisons between treatments (I,II). Repeated measurements were taken to compare drug effect between treatments (III) and time-difference within treatment groups by using two-way analysis of variance (ANOVA) (I,II,III). If statistical significance was reached, multiple comparisons were made with Fishers protected least significance (PLSD) test (I,II,III).

In study IV the different pharmacodynamic responses were analyzed using analysis of variance for crossover design with repeated measures within periods. In this analysis, a significant step effect was indicative for concentration dependent effects, and the two factor interaction sequence*period or the three factor interaction sequence*period*step indicative for differences between the two study drugs. To assess the sensitivity of the various respiratory variables to detect drug-induced respiratory depression, the analysis was continued in case of a significant concentration effect by calculating paired contrasts vs. baseline and by correcting corresponding p-values for multiple comparisons (Bonferroni correction). In addition, 95% confidence intervals were calculated for the estimated EC₅₀ values and potency ratios. Statistical computing was performed using the SAS system for Windows (Release 6.12, 1996, SAS Institute Inc., Cary, NC, USA).

In study V comparison between the study groups were performed using unpaired Student t-test. To test the significant time-effect within the study groups, a repeated measurement-linear model was used. Statistical computing was performed using the SAS system for Windows.

A p-value less than 0.05 was considered as statistically significant. Data is given as mean±SD.

8 RESULTS

8.1 Respiratory effects

8.1.1 Effects on ventilation (V_E and V_A)

A single bolus of fentanyl 2 $\mu\text{g}/\text{kg}$ decreased V_E and V_A significantly ($p<0.05$) (I). Adding ketamine 0.25 mg/kg to fentanyl attenuated this decrease significantly ($p<0.05$). A single bolus of morphine 0.07 mg/kg decreased V_A significantly up to 15 minutes after the injection ($p<0.05$), whereas a higher dose of morphine 0.14 mg/kg decreased V_A up to 20 minutes after the injection ($p<0.05$) (III). The initial decrease in V_A after oxycodone 0.14 mg/kg was significantly deeper than after morphine, from 4.9 l/min to 2.9 l/min, during the pain stimulus ($p<0.05$). During escalating plasma pseudo-steady state alfentanil and fentanyl concentrations V_E decreased similarly during both infusions (IV). A significant decrease ($p<0.05$) was noted at targeted plasma concentration level of 31.5 ng/ml for alfentanil and 0.63 ng/ml for fentanyl. The calculated apparent EC_{50} of V_E for alfentanil was 234 ± 57 ng/ml and for fentanyl 6.1 ± 1.4 ng/ml , with a potency ratio of 1:39. A significant decrease in V_A was detected at alfentanil concentration of 12.5 ng/ml and at fentanyl concentration of 0.25 ng/ml ($p<0.05$). The total decreases in V_A and V_E during alfentanil and fentanyl treatments were highly significant ($p<0.001$). The measured and predicted alfentanil and fentanyl concentrations are presented in Figure 2.

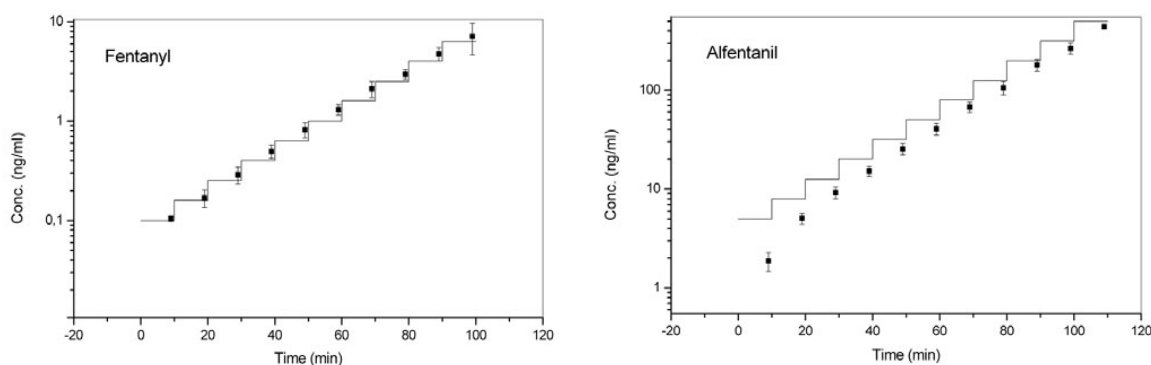


Figure 2. Targeted (solid lines) and mean (SD) measured (filled squares) fentanyl and alfentanil plasma concentrations in study IV

8.1.2 Effects on breathing pattern

Respiratory rate decreased after opioid administration. Fentanyl 2 µg/kg with or without ketamine decreased respiratory rate significantly ($p<0.05$) (I). Tramadol 150 mg IV bolus increased respiratory rate transiently ($p<0.05$), but infusion of 250 mg tramadol in 3 hours did not affect respiratory rate (II). No decrease in respiratory rate was detected at 5 minutes after a i.v. bolus of 112.5 mg pethidine, however during the 3 hours infusion of 187.5 mg pethidine respiratory rate decreased slightly but significantly ($p<0.05$). After morphine 0.07 mg/kg, morphine 0.14 mg/kg and oxycodone 0.14 mg/kg respiratory rate was significantly decreased ($p<0.05$), with a greatest decrease after oxycodone administration ($p<0.05$) (III). When oxycodone 0.14 mg/kg was given to trauma patients, the decrease in respiratory rate was minimal and did not reach significance (V). Escalating alfentanil and fentanyl concentrations caused a significant decrease in respiratory rate at a concentration level of 20 ng/ml for alfentanil and 0.4 ng/ml for fentanyl onwards ($p<0.05$) (IV). The total decrease in respiratory rate during these infusions were highly significant ($p<0.001$). The calculated apparent EC_{50} for respiratory rate was 195 ± 101 for alfentanil and 3.5 ± 1.4 for fentanyl.

V_T was increased after opioid administration. Fentanyl 2 µg/kg with and without ketamine 0.25 mg/kg increased V_T significantly ($p<0.05$) (I). Tramadol given as bolus increased V_T , but during tramadol infusion V_T was significantly decreased ($p<0.05$). Bolus administration of pethidine decreased V_T , but during pethidine infusion, V_T was significantly increased ($p<0.05$) (II). V_T was not significantly affected in trauma patients treated with oxycodone 0.14 mg/kg (V). During fentanyl infusion an increase in V_T was noted at plasma concentration of 2.5 ng/ml and with alfentanil at plasma concentration of 125 ng/ml onwards ($p<0.05$). The total increase in V_T during these infusions was highly significant ($p<0.001$) (IV). All opioids given in studies II,IV affected breathing pattern significantly as described in Table 4.

Table 4. *Effects of opioid on breathing pattern*

Drug	V_T/T_I	T_I/T_{TOT}	RC%
Tramadol bolus	0	0	ND
inf	0	decreased	ND
Pethidine bolus	0	0	ND
inf	increased	decreased	ND
Alfentanil inf	increased	ND	increased
Fentanyl inf	increased	ND	increased

ND = not defined

V_T/T_I = mean inspiratory flow

T_I/T_{TOT} = inspiratory duty cycle RC% = the proportion of ventilation that can be attributed to rib cage expansion

8.1.3 Effects on arterial blood gases

Fentanyl 2 µg/kg caused a clear decrease in PaO₂ ($p < 0.05$), the decrease being similar with and without ketamine 0.25 mg/kg (I). Morphine 0.07 mg/kg as well as 0.14 mg/kg decreased PaO₂ only slightly, although significantly ($p < 0.05$), whereas oxycodone 0.14 mg/kg caused a more profound decrease in PaO₂, the lowest value being 9.7 kPa 4 minutes after drug injection (III). When oxycodone 0.14 mg/kg was given to trauma patients, PaO₂ remained within normal values in patients breathing room air. In patients breathing 40% oxygen PaO₂ was increased well above baseline level (V). PaO₂ was decreased significantly from baseline values at alfentanil plasma concentration of 50 ng/ml and fentanyl plasma concentration of 1 ng/ml (IV). Fentanyl 2 µg/kg with or without ketamine 0.25 mg/kg increased PaCO₂ significantly, with a peak effect at 15 minutes post injection (I).

Tramadol 250 mg given in 3-hour infusion increased PaCO₂ slightly, but significantly ($p < 0.05$) (II). The increase of PaCO₂ during pethidine 187.5 mg infusion was greater compared to tramadol ($p < 0.05$). Both morphine 0.07 mg/kg and 0.14 mg/kg increased PaCO₂ significantly, PaCO₂ being elevated up to 30 minutes after the injection ($p < 0.05$) (III). The increase in PaCO₂ after oxycodone 0.14 mg/kg occurred earlier than after morphine ($p < 0.05$) and was more profound ($p < 0.05$), however the values started to decrease already at 20 minutes. In trauma patients treated with 0.14 mg/kg oxycodone, PaCO₂ remained within normal limits (V). A significant increase in PaCO₂ was detected at alfentanil plasma concentration of 20 ng/ml and fentanyl plasma concentration of 0.4 ng/ml. The EC₅₀ concentration to induce a 50% increase from baseline PaCO₂ was 263 ± 54 ng/ml for alfentanil and 6.2 ± 1.5 for fentanyl.

8.1.4 Effects on arterial hemoglobin oxygen saturation

After fentanyl 2 µg/kg bolus SpO₂ decreased from 97% to 90% with placebo and to 91% when ketamine 0.25 mg/kg was added ($p < 0.05$) (I). Tramadol caused a oxygen saturation decrease from 98% to 96% during the 250 mg infusion ($p < 0.05$), whereas pethidine 112.5 mg bolus decreased oxygen saturation from 97% to 94% and during 187.5 mg pethidine infusion the lowest value was 95% ($p < 0.05$) (II). The lowest values in oxygen saturation after morphine 0.07 mg/kg and 0.14 mg/kg were 97% and 96%, respectively (III). Oxycodone 0.14 mg decreased SpO₂ more clearly. The lowest value 94% was reached at 4 and 10 minutes post injection ($p < 0.05$ from baseline). When oxycodone 0.14 mg/kg was given to trauma patients breathing room air, SpO₂ decreased to 96% (V). A significant decrease from baseline in SpO₂ was achieved at alfentanil plasma concentration 50 ng/ml and fentanyl plasma concentration of 1 ng/ml ($p < 0.05$) (IV). The total decrease in SpO₂ during alfentanil and fentanyl infusion was highly significant ($p < 0.001$).

8.2. Effects on gas exchange

Fentanyl 2 µg/kg alone decreased both VO_2 and VCO_2 significantly ($p < 0.05$ from baseline). When ketamine 0.25 mg/kg was added to fentanyl, the effect on gas exchange was opposite: VO_2 increased significantly ($p < 0.05$ from baseline), whereas VCO_2 was not affected at all (I). After morphine 0.14 mg/kg VO_2 increased significantly ($p < 0.05$), peaking at the termination of drug injection (III). The increase in VO_2 after morphine 0.07 mg/kg did not reach significance. The decrease in VO_2 after oxycodone 0.14 mg/kg was slight and insignificant. VO_2 was decreased during alfentanil and fentanyl infusions, being significantly lower compared to baseline at plasma concentrations of alfentanil 20 ng/ml and fentanyl 0.4 ng/ml ($p < 0.05$) (IV). The decrease in VCO_2 was noted at plasma concentrations of 8.0 ng/ml for alfentanil and 0.16 ng/ml for fentanyl. The total decrease in both VO_2 and VCO_2 was highly significant during both infusions ($p < 0.001$).

8.3 Hemodynamic effects

A bolus of fentanyl 2 µg/kg decreased HR significantly but did not affect MAP. Adding ketamine 0.25 mg/kg to fentanyl caused a significant increase in both HR and MAP ($p < 0.05$) (I). Tramadol did not affect hemodynamics, whereas pethidine 187.5 mg infusion slightly decreased HR from 67 ± 12 bpm to 60 ± 7 bpm ($p < 0.05$). No effect was seen in MAP during pethidine administration (II). Both morphine 0.07 mg/kg and 0.14 mg/kg caused a significant but transient increase in MAP and HR ($p < 0.05$ from baseline), peaking at termination of the bolus injection (III). Oxycodone 0.14 mg/ml decreased MAP at 30 minutes after drug injection ($p < 0.05$ from baseline), whereas HR was not affected by oxycodone. Oxycodone 0.14 mg/kg given to trauma patients did not significantly affect MAP or HR (V). Neither alfentanil nor fentanyl infusion caused any changes in HR (IV) even at high plasma concentrations, and their effects on MAP were also minor.

8.4. Effects on plasma catecholamines

Tramadol did not have any effect on plasma norepinephrine concentrations. A bolus of pethidine 112.5 mg increased plasma norepinephrine concentration significantly, this increase persisted till the end of the 187.5 mg infusion. Both morphine 0.07 mg/kg and oxycodone 0.14 mg/kg increased plasma norepinephrine slightly but significantly at 4 minutes post drug injection.

Plasma epinephrine concentrations were increased after tramadol 150 mg bolus and 250 mg infusion (II), pethidine 112.5 mg bolus and 187.5 mg infusion (II) and morphine 0.14 mg/kg bolus (III). Other treatments did not significantly affect plasma epinephrine concentrations.

8.5 Effects on plasma histamine

After bolus of morphine 0.14 mg/kg, plasma histamine concentrations were increased slightly, but statistically significantly ($p < 0.05$). The smaller dose of morphine and oxycodone did not affect the plasma histamine concentrations (III).

8.6 Effects on atelectasis formation

In study V, no clinically significant atelectasis formation was noted in any of the patients. In 3/7 patients breathing 40% oxygen and 4/6 patients breathing room air there was evidence of minimal, clinically insignificant dorsal dependent atelectasis. No effect of supplemental oxygen was noted in the Hounsfield units, which ranged from -840 ± 40 to -800 ± 20 , indicative of well aerated lung parenchyma.

8.7 Adverse effects

A bolus of fentanyl 2 $\mu\text{g/kg}$ with or without ketamine 0.25 mg/kg did not cause any euphoria, dysphoria, dizziness, and dryness of mouth or sedation (I). Tramadol treatment caused significantly more nausea compared to pethidine ($p < 0.05$) (II). Morphine 0.14 mg/kg and oxycodone 0.14 mg/kg caused significantly more euphoria compared to morphine 0.07 mg/kg and placebo ($p < 0.05$) (III). One volunteer fainted 2 hours after morphine 0.14 mg/kg administration and one volunteer vomited 60 minutes after oxycodone 0.14 mg/kg administration. However, no difference was found in the VAS scores of dysphoria and nausea between treatments. Both morphine doses, i.e. 0.07 mg/kg and 0.14 mg/kg caused redness and itching at the injection site. This was not seen after oxycodone and placebo injections. During study IV, one alfentanil infusion had to be terminated prematurely because of nausea and vomiting. In addition, one volunteer vomited after fentanyl infusion and two after alfentanil infusions. Four subjects reported itching and three subjects reported dryness of mouth after fentanyl and two after alfentanil infusions. One subject reported hallucinations during both infusions. During study V, one patient had a transient loss of P-wave in the electrocardiogram and one patient had a transient feeling of nausea.

9 DISCUSSION

9.1 Discussion of methods

In studies I to IV, a randomized and controlled cross-over design was used to control problems arising from possible interindividual variations. This design also enabled the use of relatively few subjects, as each subject served as his own control. Only healthy young adult male volunteers were studied. Female volunteers were excluded because of fear of hormonal disturbances in drug pharmacodynamics. It should also be noted that these results may not be applicable in elderly patients, patients with other hemodynamic or respiratory compromises, or patients with concomitant use of other respiratory depressant drugs.

9.1.1 Accuracy of respiratory inductive plethysmography

The respiratory inductive plethysmography used in this study has been found to be accurate (Watson et al 1988, Sackner et al 1989, Valta et al 1992, Leino et al 2001). The calibration of RIP was done semiquantitatively according to the method described by Sackner (1989) and Leino (2001). This calibration method is carried out during a brief period of natural breathing subjects lying in supine position. If a known volume reference, i.e. pneumotachometer, is not used for volume calibration as done in studies II,III, V, the relative changes in V_T and its derivatives V_E and V_T/T_I can still be tracked (Sackner et al 1989). The validity of this calibration method and the analysis of V_T is reported to be stable even for long follow-up periods (Valta et al 1992, Leino et al 2001).

There are some factors affecting the accuracy of RIP. First, the validity of V_T measurements declines with very high or low V_T (Sackner et al 1989). In the present set of studies, very low V_T -values were not seen and the high V_T -values obtained were within 145% of the calibration values (I,II,IV), therefore the validity of V_T should be appropriate. Secondly, RIP measurements of ribcage volume (RC%) displacement can overestimate the actual displacement during quiet breathing. This is due to the fact that significant portion of the total thoracic volume change during inspiration does not displace gas but accommodates a substantial increase in intrathoracic volume. It is also due to the fact that the lower part of the ribcage is not in contact with the lungs but forms part of the abdominal cavity and the motion of this area does not contribute to the changes in lung volume (Warner et al 1995). However RIP was considered by Warner (1995) to be a valid tool to measure anesthetic effects on chest wall motion, if not the actual displacement of chest wall structures. In the present set of studies, RC% was studied in conjunction with escalating plasma alfentanil and fentanyl concentrations (IV) and the value was used for detecting chest wall rigidity, i.e. decreased RC%. However, in study IV, RC% increased dose-dependently from the

baseline values, and the possibility of chest wall rigidity was therefore excluded. Thirdly, if the subjects position is changed other than horizontally during the RIP measurement, the changes in V_T may be rendered inaccurate (Warner et al 1995). This was prevented during the present studies by asking the volunteers (I–IV) and patients (V) to lie still during the experiment.

9.1.2 Accuracy of indirect calorimetry

Indirect open calorimetry is designed for both spontaneously breathing and mechanically ventilated patients. The validation of this method was done by Takala et al (1989). In canopy measurements the mean error is $3\pm 2\%$ in VCO_2 and $4\pm 2\%$ in VO_2 , with the range of VO_2 and VCO_2 being from 100 to 400 ml/min. Increasing the FiO_2 resulted in increasing error of VO_2 , with values of >0.8 being invalid. This error was prevented by keeping the FiO_2 at 0.21 (studies I–IV). Rising V_E reduces the accuracy only slightly. In the study of Takala et al (1989), VO_2 measured by indirect calorimetry was consistently larger than VO_2 measured by the Fick's principle. Despite this difference, there was a strong positive correlation between the two methods. In two other studies, the mean error for measurement of VCO_2 ranged from 1.5% to 7% and for VO_2 1.9% to 7% (Phang et al 1990, Weissman et al 1984). The risk of errors caused by leaks during the canopy measurement is relatively small since air is sucked through the canopy. In studies I, III and IV, indirect calorimetry was mostly used for the measurement of mean drug-induced changes in VO_2 and VCO_2 .

Changes in ventilatory pattern or cardiac output may lead to a new equilibrium in the body's O_2 and CO_2 stores. Both opioid-induced apnea or hypoventilation as well as drug-induced hemodynamic alteration may affect the measurements of VCO_2 and VO_2 . The effect of this fluctuation can be minimized by prolonging the measurement period. A decrease in V_E may cause a change in body CO_2 pool and decrease VCO_2 , which does not necessarily reflect a decrease in metabolic VCO_2 . However, in addition to decreasing V_E , opioids could also decrease the metabolic component of VCO_2 . In studies I, III and IV, baseline measurement were performed after a 15 to 20-minute stabilization period. The duration of other measurement periods was limited by shortness of opioid-induced changes in ventilation. However, at least 3 values, each sampled during a one minute period, were used for determination of VO_2 and VCO_2 during the studies.

Alveolar ventilation in studies I, III and IV was determined from the formula $V_A = 0.115 \times VCO_2 / PaCO_2$ (Tulla et al 1995). Calculating alveolar ventilation from $PaCO_2$ gives an estimate of the physiological dead space and this form of calculation has been validated by Kiiski et al (1991), especially when measuring the relative changes in alveolar ventilation as done in studies I, III and IV.

9.1.3 Reliability of pharmacodynamic modeling

In study IV, pharmacodynamic modeling was performed in order to evaluate the potency ratio for respiratory depression of alfentanil and fentanyl. In the model used in study IV, the rise in PaCO_2 and decrease in PaO_2 was not taken into account. Thus the apparent EC_{50} -values were not corrected for normocapnia and may therefore be biased (Bouillon et al 1999, Glass et al 1999). However, the pharmacodynamic modeling was performed in order to calculate the potency ratio of respiratory depression, and the EC_{50} values obtained in study IV were therefore called “apparent” values.

9.1.4 Suitability of methods used

In the present series of studies a non-invasive monitoring system was used for ventilatory measurements. This was done to avoid the possible problems associated with the use of nose-clips and facemasks, which are mandatory if methods such as spirometry or ventilatory challenges are used. Nose-clips and facemasks are shown to induce changes in breathing pattern: V_T decreases and respiratory rate increases with varying results to V_E and V_T/T_I , if such devices are used (Gilbert et al 1972, Weissmann et al 1984, Han et al 1997). These changes in ventilation have been attributed to irritation and stimulation of nasal mucosa (Gilbert et al 1972) or the possibility that the process of registration itself draws the subject's attention to his own breathing (Han et al 1997). The classical method to study the opioid-induced changes in ventilation is to use ventilatory challenges, mainly ventilatory response to CO_2 . These tests are valid to represent the single most important mechanism in ventilatory control. However, there are some problems associated with the ventilatory challenge to CO_2 . Firstly, there are differences in response to endogenous and exogenous CO_2 loading in vivo. Secondly, extrapolation of the linear $V_E/\text{P}_a\text{CO}_2$ back to zero V_E is not without problems (Dempsey 1976). Thirdly, increased FiCO_2 also increases cardiac index, HR and peripheral blood flow, which makes simultaneous hemodynamic measurements unreliable (Cullen et al 1974, Braune et al 1997). The increasing hypercapnia during the challenges may also cause increases in ventilation by behavioral influences to minimize unpleasant breathing sensation, not only autonomic respiratory control (Oku et al 1966). Furthermore, there is a wide variability in the slope of ventilatory response to CO_2 between individuals and it is recommended that rebreathing tests should not be repeated more frequently than once every 15 minutes (Jordan 1982, Blouin et al 1996).

Using the method of resting ventilation was also done to mimic a true clinical situation without any artificial stimulants or disturbances. While the subjects were breathing room air (I–IV), developing hypoxia and/or hypercapnia could possibly have stimulated ventilation, making the subjects tolerate higher opioid doses than expected. This was most evident with

long opioid infusions (II,IV). Therefore the study setting was not thoroughly controlled, but this was unavoidable with this form of monitoring system.

Upper airway obstruction could also contribute to ventilatory depression induced by opioids. In the present sets of studies this did not occur, evidenced by non-paradoxal chest movement monitored with RIP.

The pain stimulation used in the present set of studies (II, III) consisted of upper arm tourniquet. This stimulus was not sufficient enough to induce any increases in plasma catecholamine concentrations. In study III, MAP was increased because of the pain stimulus, but HR was not affected in either of the studies. The pain stimulus is thus considered rather weak. However, in study III it helped to differentiate the hemodynamic effects of morphine and oxycodone.

9.2 Discussion of the results

9.2.1 Respiratory effects

Pain is a considerable respiratory stimulant and counteracts the respiratory depression induced by opioids. However, a moderate or severe respiratory depression may occur despite lack of analgesia as shown by Dahan et al (2004) who quantified analgesia and respiratory depression in healthy volunteers who were given morphine 0.2 mg/kg. In the present set of studies the peak effect of morphine-induced decrease in alveolar ventilation occurred at 10 to 15 minutes after intravenous injection (III). This is well in accordance to previous data, where the clinical effects of morphine only occur after a certain time lag (Hamunen 1993, Orkin et al 1955). The respiratory depression noted after morphine 0.07 mg/kg and 0.14 mg/kg was modest: both PaO_2 and PaCO_2 were maintained within normal limits. Respiratory rate was only slightly decreased after the higher morphine dose, 0.14 mg/kg, whereas 0.07 mg/kg did not affect respiratory rate. This decrease in respiratory rate has been previously reported after morphine administration (Rigg et al 1981, Samuel et al 1977). The slight decrease in V_A and respiratory rate did not affect arterial oxyhemoglobin saturation or carbon dioxide elimination in a clinically significant manner and could thus be considered as minor changes.

Oxycodone 0.14 mg/kg given to healthy volunteers (III) affected respiration more profoundly than morphine using the same dose. Respiratory rate and V_A were decreased, peaking at 4 to 10 minutes, which is slightly earlier compared to morphine. This is in accordance to previous studies, where the onset of analgesia and respiratory depression occurs earlier with oxycodone than morphine (Kalso et al 1991, Olkkola et al 1994). However, if a similar

dose of oxycodone, 0.14 mg/kg is given to trauma patients with severe pain, respiration is not affected (V). This is in accordance to the study of Galinski et al (2005), where morphine 0.1 mg/kg was given as an analgesic for prehospital pain and no effects in respiration were detected. The patients in study V were previously healthy and no other medication was given in conjunction with the opioid. This elucidates the importance of not applying the results obtained from postoperative patients or healthy volunteers directly to patients with severe, acute pain. Especially patients with acute fractures appears to receive insufficient doses of analgesics (Lewis et al 1994, Goodacre et al 1996, Jones et al 1996). Even though the potency ratio of morphine and oxycodone was not investigated in the present set of studies, the deeper respiratory depression induced by oxycodone administration suggests that oxycodone is more potent than morphine, as earlier evidenced by Kalso et al (1991). Even though morphine has higher binding affinity to μ -receptor, the higher blood-brain barrier penetration of oxycodone versus morphine could offer an explanation for this (Lalovic et al 2006).

A bolus dose of 112.5 mg pethidine affected respiration transiently (II). The respiratory rate was not affected, but V_T decreased, resulting in a decrease in SpO_2 to low normal limits. This effect had already vanished at 30 minutes post injection. These findings are in conjunction with the study of Orkin et al (1955), in which 100 mg an intravenous bolus dose of pethidine given to healthy volunteers markedly decreased V_T , which returned near to normal within 15 minutes. The respiratory rate did not fall after the pethidine bolus. In a study of Tarkkila et al (1998), a bolus dose of pethidine 0.6 mg/kg was given to intubated patients breathing halothane in 70% nitrous oxide and oxygen. 0.6mg/kg of pethidine decreased both respiratory rate and V_T . The decrease in respiratory rate can be explained by the simultaneous use of nitrous oxide and halothane. When 187.5 mg of pethidine was given as a 3-hour infusion, the opposite effect occurred, V_T increased and respiratory rate decreased with little effect on SpO_2 . In previous literature both kinds of effects have been documented, the net result being a slight respiratory depression. V_T/T_b , an indicator of respiratory drive (Orkin et al 1955) was increased during pethidine infusion. This could be a result of a rise in $PaCO_2$, which stimulates ventilation. Pethidine is documented to decrease ventilatory drive, which did occur after bolus dose of pethidine, but not during the 3-hours infusion (Kryger et al 1976).

A bolus dose of 2 μ g/kg fentanyl decreased V_E by decreasing respiratory rate, whereas V_T was concomitantly increased (I). The peak effect of this occurred within 5 minutes after the injection and lasted approximately 30 minutes. The timing of respiratory depression is consistent with previous literature where the time to peak effect is described to occur within 3.6 to 4.5 minutes (Scott et al 1985, Ebling et al 1990, Scholz et al 1996). However, longer time lag for peak effect has also been documented (Kaufman et al 1979). In the study of McClain et al (1980), a fentanyl bolus 3.2–6.4 μ g/kg decreased respiratory rate markedly, but nearly normal values were already obtained in 15 minutes after the injection. When fentanyl was given as a long-lasting, computer-controlled infusion with escalating

plasma fentanyl concentrations, a significant change in respiratory variables occurred at plasma concentrations between 0.25–2.5 ng/ml (IV). V_T was increased and respiratory rate decreased similarly as with the bolus injection of fentanyl (II). However, the subjects were still breathing at plasma concentrations of 4.0 ng/ml. This plasma concentration is surprisingly high compared to many of those of previous studies, where the threshold of spontaneous ventilation is described to be as low as 1.5 ng/ml (Andrews et al 1983, Cartwright et al 1983, Clotz et al 1991, Shafer et al 1991). There could be several reasons explaining this. Along the infusion, hypoxia and hypercarbia were developed. These both act as potent respiratory stimulants and counteract the respiratory depression induced by fentanyl. This is supported by preserved V_T/T_P , which suggests well maintained respiratory drive. Also, acute opioid tolerance might develop during the opioid infusion (Guignard et al 2000, Scamman et al 1984). Recently, a mathematical model for fentanyl-induced respiratory depression was introduced by Magosso et al (2004). In this model, previous literature (including study IV) of respiratory depression caused by fentanyl was taken into account and a mathematical model describing this phenomenon was produced. In this model, the effect of fentanyl on ventilatory control has been mimicked by multiplying the peripheral and central chemoreceptor gain by an attenuation factor, which depends on opioid plasma concentration.

The effects of alfentanil infusion, given as computer-controlled infusion with escalating plasma alfentanil concentrations, closely resembled those of fentanyl (IV). A significant respiratory depression was noted at plasma concentrations between 12.5–125 ng/ml. The volunteers were still breathing at plasma levels of 200 ng/ml. Recovery of spontaneous ventilation after surgery is reported to occur with plasma concentrations of 125 to 226 ng/ml (Ausems et al 1988, Clotz et al 1991, Shafer et al 1991). The same reasons explaining spontaneous ventilation with high plasma concentrations of fentanyl are also applicable to alfentanil. Muscle rigidity has been postulated to be one of factors contributing to alfentanil induced respiratory depression. No muscle rigidity was seen during alfentanil infusion, as evidenced by increasing RC%, despite high plasma concentrations. Previous literature mostly connects the alfentanil-induced rigidity to rapid injection, but muscle rigidity is also seen during infusions (Benthuysen et al 1986).

If the respiratory effects of alfentanil and fentanyl are compared during the infusions, no major differences can be found. Only V_A and SpO_2 decreased sooner with fentanyl, all other variables showed similar time course. In previous literature the respiratory depression is described to be similar with alfentanil and fentanyl (Hill et al 1990), but alfentanil has also been suggested to cause less respiratory depression (Andrews et al 1983, Scamman et al 1984, White et al 1986). The changes in breathing pattern were similar to those seen in study II with pethidine infusion (Table 4). Also, in the studies of Persson et al (1999) and Leino et al (1999), a long infusion of opioid decreases respiratory rate and the timing of respiration, while respiratory drive is either increased or not affected at all. Opposite results have also been found, though (Cartwright et al 1998). In the study of Bouillon et al

(2003), alfentanil caused a decrease in V_E and increased the variation of V_T , i.e. disturbed the regularity of breathing. The potency-ratio of alfentanil and fentanyl induced respiratory depression (1:39–1:51) was calculated in study IV to be similar to analgesic potency ratio or slowing of EEG studied elsewhere (Scott et al 1985, 1987, Hill et al 1990, Glass et al 1993, Westmoreland et al 1994, Gambus et al 1995).

The respiratory depression caused by tramadol was minimal (II). Both V_T and respiratory rate were preserved after tramadol 150 mg bolus as well as 250 mg given as 3-hour infusion. SpO_2 as well as $PaCO_2$ were also maintained within normal limits throughout the study. These findings are in line with previous studies, where the respiratory effects of tramadol are found to be negligible (Radbruch et al 1996, Tarkkila et al 1998, Grond et al 2004). However, the total dose given in this study, 400 mg, is the daily maximum dose recommended and no previous study has evaluated the effects of this dose to respiration.

A low dose of ketamine, 0.25 mg/kg, was combined with fentanyl in order to evaluate whether it could counteract the opioid-induced respiratory depression. The respiratory effects of ketamine vary in previous literature, from respiratory depression to respiratory stimulation (Hui et al 1955, Corssen et al 1966, Soliman et al 1975, Mankikian et al 1986, Reich et al 1989). Ketamine attenuated the decrease which fentanyl caused in V_E as well as V_A , but it did not have any effect on the hypoxia or hypercarbia caused by fentanyl. The increase in VO_2 could at least partly explain the reason why PaO_2 and SpO_2 were not affected, even though ketamine was added to fentanyl. In the study of Persson et al (1999) ketamine or placebo was delivered with computer controlled infusion together with computer controlled alfentanil infusion. V_E , T_I/T_{TOT} , respiratory rate and SpO_2 were all elevated to baseline level when ketamine was added to alfentanil compared to using alfentanil alone. The possible reason for this discrepancy in results is that in the study of Persson et al (1999), both drugs were given as slow infusions with slowly escalating plasma drug concentrations, while in study I both ketamine and fentanyl were injected as a bolus, thus resulting in a very high plasma drug concentration. In the study of Persson et al (1999), hemodynamics were not affected by ketamine and VO_2 was not measured. All these older studies were performed with racemic ketamine. Recently, the S (+)-enantiomer of ketamine, i.e. S(+)-ketamine, has been available. S(+)-ketamine is twice as potent as the racemic mixture (Kohrs et al 1998). In an animal model S(+)-ketamine has been shown to induce respiratory depression. Direct comparison of racemic and S(+)-ketamine in respect to respiratory depression has not been evaluated (Kohrs et al 1998, Sarton et al 2001).

As a rule, all opioids induce respiratory depression to some degree. However, there are aspects which need to be taken into account when comparing the results of different studies. First, the mode of administration, bolus or injection affects the results. Slow opioid infusions, even with large net dosage are well tolerated in respect of respiratory depression (II,IV). Respiratory depression is deeper when an opioid is given as a bolus (II), this being due to instantly high plasma concentrations. Secondly, when comparing studies where

opioid-induced respiratory depression is studied, the mode of measurement needs to be taken into account. Different results can be obtained with invasive, i.e. rebreathing, methods and non-invasive methods. Thirdly, the setting where the opioid is given and the use of concomitant depressant drugs, i.e., postoperatively after anesthesia, to patients with acute pain (V) or to healthy volunteers (I–IV), all affect the developing respiratory depression. Even considerably large bolus doses can be given to hemodynamically stable patients with acute pain without any respiratory depression (V). These results may be of benefit when treating patients with acute pain in emergency situations. Also, if respiratory depression does occur, patients are still responsive to commands and can be instructed to breathe.

9.2.2 Hemodynamic effects

All opioids are considered to be hemodynamically stable. However, minor bradycardia, which cannot be considered as baroreceptor action might be evident after opioid administration (Fukuda 2006). Morphine 0.07 and 0.14 mg/kg given to healthy volunteers induced a transient, but clear hemodynamic stimulation (III). Both doses of morphine increased MAP as well as HR, which phenomenon was not shown in previous human studies. This increase was very short lasting and might not be found if the time point of measurement is postponed for more than a few minutes after injection. The classical effect of morphine on hemodynamics in previous literature is hypotension accompanied by tachycardia (Table 2). However, morphine is often studied in conjunction with cardio depressant drugs, such as anesthetics or beta-blockers. According to previous animal studies, the latter combination abolishes the stimulatory effect of morphine and turns it into hypotension and tachycardia. (Kayaalp et al 1966, Vatner et al 1975, Wallenstein et al 1979). In the study of Pfeiffer et al (1983), μ -agonists selectively injected intracerebroventricularly in rats, induce cardiovascular stimulation with low doses and bradycardia with high doses as well. In a recent study of Carter et al (2002) i.v. morphine given to healthy volunteers induced an increase in MAP and sympathetic nerve activity. Zelis et al (1974) have measured the forearm venous tone in human subjects given 15 mg iv morphine. The initial reaction to morphine was a profound vasoconstriction, which subsided in 5 minutes to venodilatation. This initial vasoconstriction occurred parallel to hemodynamic stimulation in study III.

The hemodynamic effects of oxycodone 0.14 mg/ml were minimal (III). When given to healthy volunteers oxycodone did not affect HR, but a slight decrease in MAP was noted. When given to acutely traumatized patients, oxycodone decreased MAP slightly but non-significantly and had no effect on HR (V). The hemodynamic effects of oxycodone are very little studied, but the results of these studies verify the preliminary assumption of hemodynamic stability after oxycodone administration (Takki et al 1973, Olkkola et al 1994). This gives oxycodone a certain benefit compared to morphine.

Pethidine-induced hemodynamic effects vary in different studies, the typical effect being chronotropy with simultaneous hypotension (Flacke et al 1985, Takki et al 1973). In the study of Flacke et al (1985), 5mg/kg of pethidine caused clear tachycardia and hypotension. However, these patients received diazepam and droperidol prior to pethidine administration, which most likely explains the hemodynamic result. In the present set of studies when pethidine was given as 112.5 mg (approximately 1.5mg/kg) i.v. bolus, a slight increase in both HR and MAP was noted (II). This effect did not reach significance though. In the study of Hamunen (1993), no changes in HR or MAP were noted when pethidine was given postoperatively to children. Also in the study of Tarkkila et al (1998), pethidine caused insignificant decrease in HR and MAP, when given in conjunction with halothane anesthesia. In study II, when 187.5 mg of pethidine was infused as 3-hour infusion, MAP remained stable, but HR was significantly reduced showing a classical μ -agonist effect. A large amount of pethidine can thus be injected to previously healthy subjects without any significant hemodynamic compromises.

Hemodynamics has been reported to remain stable after both fentanyl and alfentanil administration (Scott et al 1985, Bailey et al 2000, Fukuda 2005). In a recent study of Lessa et al (2004), high doses of fentanyl given to rats seemed to be hemodynamically stable and even elicit significant cardioprotective effects in a model of arrhythmia. A slight bradycardia is documented after fentanyl and alfentanil administration. When 2 μ g/kg of fentanyl was given as a single bolus, HR was transiently decreased, whereas MAP remained at baseline level (I). During long, computer-controlled infusions of fentanyl and alfentanil, both HR and MAP remained stable (IV). The developing hypercarbia or hypoxia could have counteracted the classical μ -agonist effect, bradycardia.

Tramadol did not have much effect on hemodynamics, both mean arterial pressure and heart rate were unaffected despite a large dose of tramadol infused (II). This is well in line with the results of previous studies (Radbruch et 1996, Tarkkila et al 1998, Grond et al 2004).

The addition of a small dose of ketamine to fentanyl, significantly altered the hemodynamic response of fentanyl alone (I). Both MAP and HR were elevated when ketamine was used. These effects of ketamine are well known from previous literature and are thought to be related to centrally mediated catecholamine release (Corssen et al 1966, Traber et al 1968, Tweed et al 1972, Ivankovich et al 1974). Even if a very small dose of ketamine was used and it was done in conjunction with a moderate dose of a negative chronotrop, fentanyl, ketamine still showed these characteristic stimulatory effects. In the study of Persson et al (1999), ketamine was given together with alfentanil as computer controlled infusions and no change in either MAP or HR was noted when ketamine was added to alfentanil.

9.2.3 Effects on gas exchange

Morphine-induced cardiovascular stimulation was accompanied by a transient increase in VO_2 (III). This was clearly evident with 0.14 mg/kg of morphine and has not been reported in any of the previous studies. While ventilation was not increased at this time point, the change in VO_2 is most probably due to metabolic increase in oxygen consumption. In the study of Orkin et al (1955) 10 mg i.v. morphine caused a slight but no significant rise in oxygen uptake, as calculated from the reduction in volume of spirometer drum. In the study of Jennet et al (1968) morphine was given as 10mg/ 70 kg i.v. bolus and VO_2 was measured with spirometer and showed a decrease 5–10 min after injection. No values were measured immediately after drug injection, which is why the possible increase in VO_2 could have been missed. Although VO_2 measured with Deltatrac reflects whole body VO_2 , the increase in HR indicates that myocardial VO_2 might also be transiently increased. However, it has been suggested that morphine might have some cardio protective action, which is mediated through δ -receptor (Bailey et al 2000, Kato et al 2002, Lessa et al 2004, Fukuda 2005). Oxycodone had no effect on VO_2 in healthy volunteers (III). VO_2 was slightly decreased after oxycodone, which probably reflects hypoventilation. Fentanyl 2 $\mu\text{g/kg}$ bolus decreased VO_2 transiently (I), while VO_2 was gradually decreased during fentanyl infusion with escalating plasma concentrations (IV). Both these effects are most probably due to decreased respiratory rate and hypoventilation, not necessarily true decrease in oxygen consumption. However, opioids might also decrease the metabolic component of VO_2 by reducing heart rate (Bailey et al 2000, Fukuda 2005). The effect of alfentanil infusion on VO_2 was similar to those of fentanyl.

When a small dose of ketamine, 0.25 mg/kg, was added to fentanyl, a transient increase in VO_2 was noted. This was accompanied by the hemodynamic stimulation caused by the drug combination. This increase in VO_2 resulted in similarly low blood oxygenation, as did fentanyl alone, despite more preserved V_A and V_E . The effect of ketamine on VO_2 has been well documented and is thought to be a result of increased sympathetic tone (Traber et al 1968, Tweed et al 1972).

9.2.4 Effects on plasma catecholamines

Morphine did not have any clinically significant effect on plasma catecholamine concentrations. In some previous studies similar results, i.e. no significant catecholamine release, were found after a high dose of morphine (Flacke et al 1985, Doenicke et al 1995). However, in the study of Fahmy et al (1983), 0.3 mg/kg of intravenous morphine caused a significant increase in plasma epinephrine concentrations. Tachycardia induced by morphine is thought to be a result of histamine and catecholamine release based on the observation that these

changes occur simultaneously (Fahmy et al 1983, Flacke et al 1987, Muldoon et al 1987). The effects of oxycodone on plasma catecholamines were also minimal. Epinephrine, not norepinephrine, concentration was elevated after oxycodone administration. This can be explained by mild hypoxia caused by oxycodone. Pethidine caused a significant increase in both epinephrine and norepinephrine concentrations. This has also been documented previously in the study of Flacke et al (1985). In study II, tramadol increased plasma epinephrine concentrations, but had no effect on norepinephrine concentrations. In the study of Garcia-Quetglas et al (2007), plasma epinephrine concentrations were increased after tramadol in conjunction with adverse effects, i.e., nausea and vomiting. This finding is in accordance to our results in study II.

9.2.5 Effects on plasma histamine

Plasma histamine concentrations were maintained well under 0.4 ng/ml after morphine and oxycodone administration (III). The level of histamine plasma concentration to elicit symptoms is reported to be over 1 ng/ml, with baseline level being 0.6 ng/ml (Kalinin et al 1982). Histamine infusion is reported to cause tachycardia and widening of pulse pressure, these changes being evident immediately after histamine release and vanishing quickly because of rapid clearance. (Kalinin et al 1982). In study III, the sampling for plasma histamine was done simultaneously with the hemodynamic stimulation observed, which should have detected any changes in plasma histamine concentrations. Our results differ from many previous reports concerning histamine liberation after morphine (Philbin et al 1981, Rosow et al 1982, Flacke et al 1985, Moss et al 1983, Muldoon et al 1987, Withington et al 1993, Doenicke et al 1995). The study of Warner et al (1991) however gives similar results compared to study III, with no histamine release after morphine. Their explanation to their contradictory results is that they used a more novel assay of histamine detection, double-isotope assay, instead of single-isotope assay used in the older studies (Philbin et al 1981, Rosow et al 1982, Flacke et al 1985, Moss et al 1983). In the studies of Doenicke (1995) and Withington (1993), not all subjects produced histamine release after morphine administration. It could therefore be theoretically possible that in study III, all eight volunteers were unable to liberate histamine, and repeating the same study on other volunteers would give different results. In study III, local signs of possible histamine release were seen, flare and itching was detected in all subjects after morphine administration. This local liberation of histamine has also been demonstrated also previously (Hermens et al 1985, Levy et al 1989) and is thought to originate from skin mast cells and not to be mediated through μ -receptor (Blunk et al 2004). The histamine releasing ability of oxycodone is thought to be minimal (Pöyhä et al 1992) as in study III. This was further confirmed by another study of Pöyhä et al (2004). However, Ennis (1991) has shown that porcine mast cells liberate histamine after oxycodone administration even more than after morphine administration.

The ability of opioids to induce cardiovascular changes or to liberate histamine or catecholamines still remains incompletely examined and answered. The hemodynamic changes induced by opioids seem to be influenced by the dose of opioid, the mode of administration, i.e. bolus injection or slow infusion and possible concomitant medication. High plasma concentrations in conjunction with bolus dosing produce clearer hemodynamic changes than slowly escalating plasma concentrations with infusions. If hemodynamic effects are studied on patients with beta-blocking agents or vasodilators such as droperidol, the net effect is naturally different. The different results with catecholamine and histamine release in this study compared to previous studies are more difficult to explain than the different result in hemodynamic profile. The capacity of morphine and pethidine to release histamine or catecholamine is probably not as straightforward. There might be subjects with more easily provoked histamine release, or some histamine assays might be more reliable than others. However, in the case of the present study, the truth about catecholamine and histamine release after opioid administration still remains unsettled.

9.2.6 Effects on atelectasis formation

No atelectasis formation was seen in any of the extremity trauma patients treated with oxycodone (V). In previous studies atelectasis formation and low lung volumes were seen in patients treated with respiratory depressant drugs while breathing oxygen enriched air (Rothen et al 1995, Reber et al 1996). Increased atelectasis formation is already seen with 30% oxygen, but the atelectasis formation is greater with increasing oxygen concentration, being most evident with 100% oxygen (Nunn et al 1978, Rothen et al 1995). This is considered to be associated with decreased V_T . In study V, V_T were not decreased considerably and the inspired oxygen concentration was chosen to be 40%, not higher. These factors can contribute to the fact that no atelectasis was seen in any of the patients. In the previous studies where atelectasis was seen, it caused some degree of hypoxia despite the supplemental oxygen (Mackersie et al 1991, Rothen et al 1995). All our patients breathing 40% oxygen had oxygenation values well above normal, supporting the conclusion of normal lung function.

9.2.7 Limitations of the present series of studies

The results of the current series of studies must be interpreted with caution due to some experimental limitations. Healthy volunteers were used in studies I–IV. The results must therefore be carefully extrapolated to patients with underlying diseases or hemodynamic compromises. Patients with cardiovascular diseases, especially those using heart rate regulating drugs, could present different hemodynamic profile after opioid administration. Also, if hepatic or renal function is compromised, the pharmacokinetic and thus also pharmacodynamic profiles of opioids could be greatly altered. Patients with diabetes often

have impaired peripheral neuronal control and could also react differently to these drugs. The ventilatory effects of opioids could also be different in patients with pulmonary disease. And as mentioned before, O₂ administration could also have an impact on the respiratory effects of opioids. In studies I–IV each volunteer served as his own control, which allows the use of a smaller number of subjects. In study V, a relatively small number of patients (13) were studied, which might increase the risk of error of the results.

The visible respiratory depression and sedation might have obscured the double-blindness in study III, where placebo was used.

The magnitude of the norepinephrine release in studies II and III may not be reflected exactly in the concentrations from arterial blood samples. Compared to arterial blood, venous blood has been shown to contain higher concentrations of norepinephrine.

10 SUMMARY AND CONCLUSIONS

This study was performed in healthy volunteers (I–IV) and trauma patients (V). The opioids studied were fentanyl, alfentanil, morphine, oxycodone, pethidine and tramadol. Furthermore, ketamine was studied in conjunction with fentanyl. Non-invasive ventilatory measurements (RIP, indirect calorimetry) were used in order to avoid the problems depicted with respiratory challenges.

The following main conclusions can be drawn:

- All opioids studied caused a decrease in respiratory parameters. Respiratory rate, V_A and V_E decreased (I–IV), while V_T increased in most situations, except during tramadol-infusion and after bolus dose of pethidine, where it decreased (I). The respiratory depression caused by 0.14 mg/kg of oxycodone was deeper than the one caused by the same dose of morphine (III). Breathing pattern was also significantly affected after opioid administration (II,IV). An equianalgesic dose of tramadol caused markedly smaller respiratory depression compared to pethidine, when given as a iv-bolus and 3-hour iv-infusion.
- The potency ratio for respiratory depression of fentanyl and alfentanil varied from 1:39–1:51, which is similar to the analgesic potency ratio studied elsewhere.
- 0.25 mg/kg of racemic ketamine attenuated the respiratory depression caused by 2 µg/kg fentanyl. However, this occurred at the expense of increased VO_2 , which resulted in unchanged levels of PaO_2 and SpO_2 .
- Intravenous morphine caused a transient hemodynamic stimulation, which was accompanied by increase in VO_2 . This phenomenon was not noted with the use of intravenous oxycodone. Alfentanil, fentanyl, tramadol and pethidine infusion had minimal effects on hemodynamics.
- Plasma catecholamine concentrations were increased after morphine, oxycodone, pethidine and tramadol administration. However, plasma histamine concentration was not elevated after morphine administration. Oxycodone did not affect plasma histamine level, and plasma epinephrine level was increased in conjunction with hypoxia.
- Supplemental oxygen did not cause any atelectasis when given to opioid treated trauma patients. However, patients breathing room air had a sufficient level of oxygenation, so supplemental oxygen did not add any benefits to these patients.

11 ACKNOWLEDGEMENTS

This study was carried out at the Department of Anesthesia, Turku University Central Hospital and Department of Anesthesia and Surgery, Töölö Hospital, Helsinki University Central Hospital. I wish to thank late Professor Jussi Kanto from Department of Anesthesia in University of Turku and late Professor Seppo Santavirta from Department of Orthopedics and Traumatology, University of Helsinki for providing me with the opportunity to perform these studies.

This study was supervised by Professor Per Rosenberg and Docent Olli Kirvelä. Both had their profound impact on this thesis. This study was initiated by Docent Olli Kirvelä and without his enthusiasm and collaboration these studies would never have started. I am deeply indebted to Professor Per Rosenberg, my other supervisor, for encouraging me in finishing this thesis. He is an excellent tutor and researcher, but I am privileged to know him also as an deeply empathetic and understanding colleague, without whom this thesis would never have been finished.

Professor Olli Polo and Docent Päivi Valta, the official reviewers of this thesis, are gratefully acknowledged for their constructive criticism, valuable comments for the improvement of the manuscript and for stimulating conversations during this process.

All of my co-authors are gratefully acknowledged. Professor Mika Scheinin from University of Turku and Professor Leena Tuomisto from University of Kuopio are thanked for their help and expertise in the world of catecholamines and histamine. Professor Harry Scheinin from University of Turku is greatly acknowledged for his vast scientific and clinical knowledge in clinical pharmacology and for providing me the best study of this thesis. Working with him was both stimulating and fun! Dr Markku Taittonen and Dr Kari Leino are thanked for their collaboration and for teaching me facts about indirect calorimetry and respiratory inductive plethysmography. Dr Anneli Piilonen is greatly thanked for her help and expertise and knowledge in computer tomography. Dr Markku Kallio, Hans Helenius and Lauri Sillanmäki are acknowledged for their help in statistical analyses. Elina Kahra is acknowledged for excellent technical assistance. The staff of the Emergency Department of Töölö Hospital is thanked for the collaboration in helping me with the trauma patients in study V. And finally, all those wonderful young men who took part in these studies as “healthy volunteers” are deeply thanked for their contribution in studies I–IV and for subjecting themselves for needles and nausea!

Maritta Pesonen M.A. is thanked for her kind help in reviewing the English language in this thesis.

My colleagues in the Hospital for Children and adolescents are thanked for their support during the final phase of this thesis. Some of you have encouraged me greatly!

My dearest thanks go to my family and friends. Especially I would like to thank my parents Pirkko and Sakari Närvänen for their love and encouragement, and during the dark days of life they have always been there for me. Also all other members of my family and all my dear, dear friends; I thank you so much for your support! And Henriikka, Mummy loves you the most.

This study was financially supported by grants from Turku University Hospital (EVO), Finnish Medical Society of Duodecim, Orion-Pharma and the Scientific Committee of the Finnish National Defence.

May, 2007

12 REFERENCES

- Andrews CJH, Sinclair M, Prys-Roberts C, Dye A. Ventilatory effects during and after continuous infusion of fentanyl and alfentanil. *Br J Anaesth* 1983;55:S211–216.
- Ausems ME, Hug CC, Stanski RD, Burm AGL. Plasma concentrations of alfentanil required to supplement nitrous oxide anesthesia for general surgery. *Anesthesiology* 1986;65:362–373.
- Ausems ME, Vuyk J, Hug CC, Stanski DR. Comparison of a computer-assisted infusion versus intermitted bolus administration of alfentanil as a supplement to nitrous oxide for lower abdominal surgery. *Anesthesiology* 1988;68:851–861.
- Bailey PL, Egan TD, Stanley TH. Intravenous opioid anesthetics. *Anesthesia*, 5th edition. Edited by Miller RD. New York, Churchill Livingstone, 2000:273–
- Becker HF, Polo O, McNamara SG, Berthon-Jones M, Sullivan CE. Ventilatory response to isocapnic hypoxia. *J Appl Physiol* 1995;78:696–701.
- Becker HF, Polo O, McNamara SG, Berthon-Jones M, Sullivan CE. Effect of different levels of hyperoxia on breathing in healthy subjects. *J Appl Physiol* 1996;81:1683–1690.
- Beers R, Camporesi E. Remifentanyl update. *CNS Drugs* 2004;18:1085–1104.
- Benthuyzen JL, Smith NT, Sanford TJ, Head N, Des-Silver H. Physiology of alfentanil-induced rigidity. *Anesthesiology* 1986;64:440–446.
- Blouin RT, Jeffrey BG. Ventilation and conscious sedation. *Seminars in Anaesthesia*. 1996;15:335–342.
- Blunk JA, Schmelz M, Zeck Susanne, Skov P, Likar R, Koppert W. Opioid-induced mast cell activation and vascular responses is not mediated by μ -opioid receptors: an invivo microdialysis study inhuman skin. *Anesth Analg* 2004;98:364–370.
- Boothby LA, Doering PL. Buprenorphine for treatment of opioid dependence. *Am J Health-Syst Pharm* 2007;64:266–272.
- Borgbjerg FM, Nielsen K, Franks J. Experimental pain stimulates respiration and attenuates morphine-induced respiratory depression: a controlled study in human volunteers. *Pain* 1996;64:123–128.
- Bouillon T, Schmidt C, Gartska G, Heimbach D, Stafforst D, Schwilden H, Hoeft A: Pharmacokinetic-pharmacodynamic modeling of the respiratory depressant effect of alfentanil. *Anesthesiology* 1999;91:144–155
- Bouillon T, Bruhn J, Roepcke H, Hoeft A. Opioid-induced respiratory depression is associated with increased tidal volume variability. *Eur J Anaesth* 2003;20:127–133.
- Bourke DL, Malit LA, Smith TC. Respiratory interactions of ketamine and morphine. *Anesthesiology* 1987; 66: 153–6.
- Braune S, Hetzel A, Prasse A, Dohms K, Guschlbauer B, Lueking CH. Stimulation of sympathetic activity by carbon dioxide in patients with autonomic failure compared to normal subjects. *Clin Auton Res* 1997;7:327–32.

- Brittain GJC. Dihydrohydroxycodone pectinate. *Lancet* 1959;II:544–546.
- Carter JR, Sauder CL, Ray CA. Effect of morphine on sympathetic nerve activity in humans. *J Appl Physiol* 2002;93:1764–1769
- Cartwright CR, Henson LC, Ward DS. Effects of alfentanil on the ventilatory response to sustained hypoxia. *Anesthesiology* 1998;89:612–619
- Cartwright P, Prys-Roberts C, Gill K, Dye A, Stafford M, Gray A. Ventilatory depression related to fentanyl plasma concentrations during and after anesthesia in humans. *Anesth Analg* 1983;62:966–974
- Chrubasik J, Buzina M, Schulte-Mönting J, Atanassoff P, Alon E. Intravenous tramadol for post-operative pain - comparison of intermittent dose regimens with or without maintenance infusion. *Eur J Anaesth* 1992;9:23–28.
- Clements JA, Nimmo WS. Pharmacokinetics and analgesic effect of ketamine in man. *Br J Anaesth* 1981;53:27–30.
- Clotz MA, Nahata MC. Clinical uses of fentanyl, sufentanil, and alfentanil. *Clinical Pharmacy* 1991;10:581–593.
- Corssen G, Domino E. Dissociative anesthesia: further pharmacologic studies and first clinical experience with the phenylcyclidine derivative CI-581. *Anesth Analg* 1966;45:29–39.
- Cullen DJ, Eger EI. Cardiovascular effects of carbon dioxide in man. *Anesthesiology* 1974;41:345–349.
- Dahan A, Romberg R, Tepperna L, Sarton E, Bijl H, Olofsen E. Simultaneous measurement and integrated analysis of analgesia and respiration after intravenous morphine infusion. *Anesthesiology* 2004;101:1201–1209.
- Davenport HT, Al-Khudairi D, Cox PN, Wright BM. Continuous subcutaneous pethidine for routine postoperative analgesia. *Annals of the Royal College of Surgeons of England* 1985;67:379–381.
- Dempsey JA. CO₂-response: Stimulus definition and limitations. *Chest* 1976;70:114–118.
- Desmeules JA, Piguet V, Collart L, Dayer P. Contribution of monoaminergic modulation to the analgesic effect of tramadol. *Br J Clin Pharmacol* 1996;41:7–12.
- Doenicke A, Moss J, Lorenz W, Hoerneck R. Intravenous morphine and nalbuphine increase histamine and catecholamine release without accompanying hemodynamic changes. *Clin Pharmacol Ther* 1995;58:81–89.
- Drummond GB. Comparison of decreases in ventilation caused by enflurane and fentanyl during anesthesia. *Br J Anaesth* 1983;55:825–835.
- Ebling WF, Lee EN, Stanski DR. Understanding pharmacokinetics and pharmacodynamics through computer simulation: the comparative clinical profiles of fentanyl and alfentanil. *Anesthesiology* 1990;72:650–658
- Edwards ND, Fletcher A, Cole JR, Peacock JE. Combined infusions of morphine and ketamine for postoperative pain in elderly patients. *Anaesthesia* 1993; 48: 124–7.
- Ennis M, Schneider C, Nehring E, Lorenz W. Histamine release induced by opioid analgesics: a comparative study using porcine mast cells. *Agents Actions* 1991;33:20–22.

- Fahmy NR, Sunder N, Soter NA. Role of histamine in the hemodynamic and plasma catecholamine responses to morphine. *Clin Pharmacol Ther* 1983;33:615–620.
- Flacke JW, Bloor BC, Kripke BJ, Flacke WE, Warneck CM, Van Etten AP, Wong DH, Katz RL. Comparison of morphine, pethidine, fentanyl and sufentanil in balanced anesthesia. *Anesth Analg* 1985;64:897–910.
- Flacke JW, Flacke WE, Bloor BC, Van Etten AP, Kripke BJ. Histamine release by four narcotics: a double blind study in humans. *Anesth Analg* 1987;66:723–730.
- Fukuda K. Intravenous opioid anesthetics. *Anesthesia*, 6th edition. Edited by Miller RD. New York, Churchill Livingstone, 2005:379–438.
- Fung DL, Eisele JH. Fentanyl pharmacokinetics in awake volunteers. *J Clin Pharm* 1980;20:652–658.
- Galinski M, Dolveck F, Borron S, Tual L, Van Laer V, Lardeur J-Y, Lapostolle F, Adnet F. A randomized, double-blind study comparing morphine with fentanyl in prehospital analgesia. *Am J Emerg Med* 2005;23:114–119.
- Garcia-Quetglas, Azanza JR, Sadaba B, Munoz MJ, Gil I, Campanero MA. Pharmacokinetics of tramadol enantiomers and their respective phase I metabolites in relation to CYP2D6 phenotype. *Pharmacol Res* 2007;55:122–130.
- Gambus PL, Gregg KM, Shaefer SL. Validation of the alfentanil canonical univariate parameter as a measure of opioid effect on the electroencephalogram. *Anesthesiology* 1995;83:747–756.
- Gilbert R, Auchincloss JH, Brodsky J, Boden W. Changes in tidal volume, frequency and ventilation induced by their measurement. *Journal of Applied Physiology* 1972; 33: 252–4.
- Glass PSA, Doherty M, Jacobs JR, Goodman D, Smith LR. Plasma concentration of fentanyl with 70% nitrous oxide to prevent movement at skin incision. *Anesthesiology* 1993;78:842–847.
- Glass PSA, Iselin-Chaves IA, Goodman D, Delong E, Herman DJ. Determination of the potency of remifentanyl compared with alfentanil using ventilatory depression as the measure of opioid effect. *Anesthesiology* 1999;90:1556–1563.
- Goodacre SW, Roden RK. A protocol to improve analgesia use in the accident and emergency department. *J Accid Emerg Med*. 1996;13:177–179.
- Grond S, Meuser T, Zech D, Hennig U, Lehmann KA. Analgesic efficacy and safety of tramadol enantiomers in comparison with the racemate: a randomised double-blind study with gynaecological patients using intravenous patient-controlled analgesia. *Pain* 1995;62:313–320.
- Grond S, Sablotzki A. Clinical pharmacology of tramadol. *Clin Pharmacokinet* 2004;43:879–923.
- Grossmann M, Abiose A, Tangphao O, Blaschke TF, Hoffman BB. Morphine-induced venodilatation in humans. *Clin Pharm Ther* 1996;60:554–560.
- Guignard B, Bossard AE, Coste C, Sessler DL, Lebrault C, Alfonsi P, Fletcher D, Chauvin M. Acute opioid tolerance. *Anesthesiology* 2000;93:409–417.

- Hagenouw RRPM, Bridenbaugh PO, v Egmond J, Stuebing R. Tourniquet Pain: A Volunteer Study. *Anesth Analg* 1986;65:1175–1180.
- Hamunen K. Ventilatory effects of morphine, pethidine and methadone in children. *Br J Anaesth* 1993;70:414–418.
- Han JN, Stegen K, Cauberghe M, Van de Woestijne. Influence of awareness of the recording of breathing on respiratory pattern in healthy humans. *Eur Resp J* 1997;10:161–166.
- Hermens JM, Ebertz JM, Hanifin JM, Hirshman CA. Comparison of histamine release in human skin mast cells induced by morphine, fentanyl and oxymorphone. *Anesthesiology* 1985;62:124–129.
- Hill H, Chapman C, Saeger L, Bjurström R, Walter MH, Schoene RB, Kippes M. Steady-state infusions of opioids in human. II. Concentration-effect relationships and therapeutic margins. *Pain* 1990; 43: 69–79.
- Hirota K, Lambert DG. Editorial. Ketamine: its mechanism(s) of action and unusual clinical uses. *Br J Anaesth* 1996;77:441–444.
- Hoeche M, Duka T. Opiates increase plasma catecholamines in humans. *Psychoneuroendocrinology* 1993;18:141–148.
- Hui TW, Short TG, Hong W, Suen T, Gin T, Plummer J. Additive interactions between propofol and ketamine when used for anesthesia induction in female patients. *Anesthesiology* 1995;82:641–648.
- Ivanikovich AD, Miletich DJ, Reimann C, Albrecht R, Zahed B. Cardiovascular effects of centrally administered ketamine in goats. *Anesth Analg* 1974; 53: 924–31.
- Jennet S, Barker JG, Forrest JB. A double-blind controlled study of the effects on respiration of pentazocine, phenoperidine and morphine in normal man. *Br J Anaesth* 1968;40:864.
- Jones JS, Johnson K, McNinch M. Age as a risk factor for inadequate emergency department analgesia. *Am J Emerg Med*. 1996;14:157–160.
- Jordan C. Assessment of the effects of drugs on respiration. *Br J Anaesth*. 1982;54:763.
- Kaliner M, Shelhamer JH, Ottesen EA. Effects of infused histamine: correlation of plasma histamine levels and symptoms. *J Allergy Clin Immunol* 1982;69:283–289.
- Kalso E, Pöyhkä R, Onnela P, Linko K, Tiegerstedt I, Tammisto T. Intravenous morphine and oxycodone for pain after abdominal surgery. *Acta Anaesth Scand* 1991;35:642–646.
- Kato R, Foëx P. Myocardial protection by anesthetic agents against ischemia-reperfusion injury: an update for anesthesiologists. *Can J Anesth* 2002;48:777–791.
- Kaufman RD, Aqlah KA, Bellville JW. Relative potencies and durations of action with respect to respiratory depression of intravenous pethidine, fentanyl and alphaprodine in man. *J Pharmacol Exp Ther* 1979;208:73–79.
- Kayaalp SO, Kaymakçalan S. A comparative study of the effects of morphine in unanaesthetized and anaesthetized cats. *Br J Pharmacol* 1966;26:196–204.

- Kayser V, Besson J-M, Guildbaud G. Evidence for noradrenergic component in the antinociceptive effect of the analgesic agent tramadol in an animal model of clinical pain, the arthritic rat. *Eur J Pharmacol* 1992;224:83–88.
- Keats AS, Girgis KZ. Respiratory depression associated with relief of pain by narcotics. *Anesthesiology* 1968;29:1006–1013.
- Kiiski R, Takala J, Eissa T. Measurement of alveolar ventilation and changes in dead space by indirect calorimetry during mechanical ventilation: A laboratory and clinical validation. *Crit Care Med* 1991;19:1303–1309.
- Kiiski R, Takala J. Hypermetabolism and efficiency of CO₂ removal in acute respiratory failure. *Chest* 1994;105:1198–1203.
- Kohrs R, Durieux ME. Ketamine: teaching an old drug new tricks. *Anest Analg* 1998;87:1186–1193.
- Konno K, Mead J. Measurement of the separate volume changes of rib cage and abdomen during rebreathing. *J Appl Physiol* 1967;22:407–422.
- Kryger MH, Yacoub O, Dosman J, Macklem PT, Anthonisen NR. Effect of pethidine on occlusion pressure responses to hypercarbia and hypoxia with or without external inspiratory resistance. *Am Rev Resp Dis* 1976;114:333–340.
- Lalovic B, Kharasch E, Hoffer C, Risler L, Liu-Chen L-Y, Shen DD. Pharmacokinetics and pharmacodynamics of oral oxycodone in healthy human subjects: Role of circulating active metabolites. *Clin Pharm Ther* 2006;79:461–479.
- Lee CR, McTavish D, Sorkin EM. Tramadol. A preliminary review of its pharmacodynamics and pharmacokinetic properties, and therapeutic potential in acute and chronic pain states. *Drugs* 1993;46:313–340.
- Lehmann KA. Tramadol for the management of acute pain. *Drugs* 1994;47(S1):19–32.
- Leino K, Mildh L, Lertola K, Seppälä T, Kirvelä O. Time course of changes in breathing pattern in morphine- and oxycodone-induced respiratory depression. *Anaesthesia* 1999;54:835–840.
- Leino K, Nunes S, Valta P, Takala J. Validation of a new respiratory inductive plethysmograph. *Acta Anaesth Scan* 2001; 45:104–111.
- Lessa MA, Rodrigues E, Tibirica E. Cardioprotective action of fentanyl in a model of central sympathetic overactivity in rabbits: antiarrhythmic and anti-ischemic effects. *Acta Anaesth Sacnd* 2004; 48:1115–1122.
- Levy JH, Brister NW, Shearin A, Ziegler J, Hug CC, Adelson DM, Walker BF. Wheal and flare responses to opioids in humans. *Anesthesiology* 1989;70:756–760.
- Levänen J, Mäkelä M-L, Scheinin H. Dexmedetomidine premedication attenuates ketamine-induced cardiostimulatory effects and postanesthetic delirium. *Anesthesiology* 1995;82:1117–1125.
- Lewis LM, Lasater LC, Brooks CB. Are emergency physicians too stingy with analgesics? *South Med J*. 1994;87:7–9.
- Lowenstein E, Hallowell P, Levine FH, Daggert WM, Austen WG, Laver MB. Cardiovascular response to large doses of intravenous morphine in man. *N Engl J Med* 1969;281: 1389–1393.

- Lundquist H, Hedenstierna G, Strandberg Å, Tockis L, Brismar B. CT-assessment of dependent lung densities in man during general anaesthesia. *Acta Radiologica*. 1995;36:626–632.
- Lötsch J. Pharmacokinetic-pharmacodynamic modeling of opioids. *J Pain Symptom Manage* 2005a;29:S90–S103.
- Lötsch J. Opioid metabolites. *J Pain Symptom Manage* 2005b;29:S90–S103.
- Mackersie RC, Karagianes TG, Hoyt DB, Davis JW. Prospective evaluation of epidural and intravenous administration of fentanyl for pain control and restoration of ventilatory function following multiple rib fractures. *J Trauma*. 1991;31:443–451.
- Magosso E, Ursino M, van Oostrom JH. Opioid-induced respiratory depression: a mathematical model for fentanyl. *IEEE Trans Biomed Eng* 2004;51:1115–1128.
- Mankikian B, Cantineau JP, Sartene R, Viars P. Ventilatory pattern and chest wall mechanics during ketamine anesthesia in humans. *Anesthesiology* 1986; 65: 492–9.
- Maxwell C. Sensitivity and accuracy of the visual analogue scale: a psycho-physical classroom experiment. *Brit J Clin Pharmacol* 1978;6:15–24.
- McClain DA, Hug CC. Intravenous fentanyl kinetics. *Clin Pharmacol Ther* 1980;28:106–114.
- McClain DA, Hug DD. Pharmacodynamics of opiates. *Int Anesthesiol Clin* 1984;4:75–94.
- McDonnell TE, Bartkowski RR, Williams JJ. ED₅₀ of alfentanil for induction of anesthesia in unpremedicated young adults. *Anesthesiology* 1984;60:136–140.
- Meriläinen PT. Metabolic monitor. *Int J Clin Monit Comput* 1987;4:167–177.
- Meriläinen PT. Gas and ventilatory monitoring: measurement and application. *J Cardiothorac Vasc Anesth* 2000;14:718–725.
- Michiels M, Hendriks R, Heykants J. Radioimmunoassay of the new opiate analgesic alfentanil and sufentanil. Preliminary pharmacokinetic profile in man. *J Pharm Pharm* 1983;35:86–93.
- Milic-Emili J. Recent advances in clinical assessment of control of breathing. *Lung* 1982;160:1–17.
- Milledge JS, Scott FD. Inductive plethysmograph- a new respiratory transducer. *J Physiol* 1977;267:4–7.
- Morel DR, Forster A, Gemperle M. Noninvasive evaluation of breathing pattern and thoraco-abdominal motion following the infusion of ketamine or droperidol in humans. *Anesthesiology* 1986; 65: 392–8.
- Moss J, Rosow CE. Histamine release by narcotics and muscle relaxants in humans. *Anesthesiology* 1983;59:330–339.
- Muldoon SM, Freas W, Mahla ME, Donlon MA. Plasma histamine and catecholamine levels during hypotension induced by morphine and compound 48/80. *J Cardiovasc Pharm* 1987;9:578–583.
- Muneyuki M, Ueda Y, Urabe N, Takeshita H, Inamoto A. Postoperative pain relief and respiratory function in man. *Anesthesiology* 1969;29:304–313.

- Neidhart P, Burgener MC, Schwieger I, Suter PM. Chest wall rigidity during fentanyl- and midazolam-fentanyl induction: ventilatory and haemodynamic effects. *Acta Anaesth Scand* 1989;33:1–5.
- Nishino T, Shimoyama N, Ide T, Isono S. Experimental pain augments experimental dyspnea, but not vice versa in human volunteers. *Anesthesiology* 1999;91:1633–1638.
- Nunn JF, Williams IP, Jones JG. Detection and reversal of pulmonary absorption collapse. *Br J Anaesth*. 1978;50:91–100.
- Oku Y, Saidel GM, Cherniack NS, Altose MD. Effects of willful ventilatory control on respiratory sensation during hypercapnia. *Respiration* 1966;63:137–143.
- Olkola KT, Hamunen K, Seppälä T, Maunuksela E-L. Pharmacokinetics and ventilatory effects of intravenous oxycodone in postoperative children. *Br J Clin Pharmacol* 1994;38:71–76.
- Orkin LR, Egge RK, Rovenstine EA. Effect of nisentil, pethidine and morphine on respiration in man. *Anesthesiology* 1955;16:699–707.
- Peat SJ, Hanna MH, Woodham M, Knibb AA, Ponte J. Morphine-6-glucuronide: effects on ventilation in normal volunteers. *Pain* 1991;45:101–104.
- Persson J, Scheinin H, Hellström G, Björkman S, Götharson E, Gustafsson LL. Ketamine antagonises alfentanil-induced hypoventilation in healthy male volunteers. *Acta Anaesth Scand* 1999;43:744–752.
- Pfeiffer, Feuerstein G, Zerbe RL, Faden AI, Kopin IJ. μ -Receptors mediate opioid cardiovascular effects at anterior hypothalamic sites through sympatho-adrenomedullary and parasympathetic pathways. *Endocrinology* 1983;113:920–938.
- Phang PT, Rich T, Ronco J. A validation and comparison study of two metabolic monitors. *JPEN* 1990;14:259–261.
- Philbin DM, Moss J, Akins CW, Rosow CE, Kono K, Schneider RC, Ver Lee TR, Savarese JJ. The use of H₁ and H₂ histamine antagonists with morphine anesthesia: a double-blind study. *Anesthesiology* 1981;55:292–296.
- Pugsley MK. The diverse molecular mechanisms responsible for the actions of opioids on the cardiovascular system. *Pharmacol & Ther* 2002;93:51–75.
- Pöyhiä R, Kalso E, Seppälä T. Pharmacodynamic interactions of oxycodone and amitriptyline in healthy volunteers. *Curr Ther Res* 1992;51:739–749.
- Pöyhiä R, Seppälä T. Liposolubility and Protein Binding of Oxycodone In Vitro. *Pharmacology & Toxicology* 1994;74:23–27.
- Pöyhiä R, Hynynen M, Seppälä T, Roine RO, Verkkala K, Olkkola KT. Pharmacodynamics and pharmacokinetics of high-dose oxycodone infusion during and after coronary artery bypass grafting. *J Cardiothorac Anesth* 2004;18:748–754.
- Radbruch L, Grond S, Lehman KA. A risk-benefit assessment of tramadol in the management of pain. *Drug safety* 1996;15:8–29.
- Read DJC, Leigh J. Blood-brain tissue P_{CO2} relationships and ventilation during rebreathing. *J Appl Physiol* 1967;23:53–70.
- Reber A, Engberg G, Wegenius G, Hedenstierna G. Lung areation. *Anaesthesia*. 1996;51:733–737.

- Rebuck AS. Measurement of Ventilatory response to CO₂ by rebreathing. *Chest* 1976;70:118–121.
- Reich DL, Silvay G. Ketamine: an update on the first twenty-five years of clinical experience. *Can J Anaesth* 1989;36:186–197.
- Rigg JRA, Rondi P. Changes in rib cage and diaphragmatic contribution to ventilation after morphine. *Anesthesiology* 1981;55:507–514.
- Roerig DL, Kotrly KJ, Vucins EJ, Ahlf SB, Dawson CA, Kampine JP. First pass uptake of fentanyl, pethidine and morphine in the human lung. *Anesthesiology* 1987;67:466–472.
- Rosow CE, Moss J, Philbin DM, Savarese JJ. Histamine release during morphine and fentanyl anesthesia. *Anesthesiology* 1982;56:93–96.
- Rothen HU, Sporre B, Engberg G, Wegenius G, Reber A, Hedenstierna G. Prevention of atelectasis during general anaesthesia. *Lancet*. 1995;345:1387–1391.
- Roytblat L, Levy J, Katz J, Goldstein J, Gesztes T. Balanced Anesthesia: Low-dose ketamine/neuroleptanalgesia. *Current Therapeutic Research* 1986; 40: 646–52.
- Sackner MA, Watson H, Belsito AS, Feinerman D, Suarez M, Gonzales G, Bizousky F, Krieger B. Calibration of respiratory inductive plethysmography during natural breathing. *J Appl Physiol*. 1989; 66; 410–420.
- Samuel IO, Clarke RS, Dundee JW. Some circulatory respiratory effects of morphine in patients without pre-existing cardiac disease. *Br J Anaesth* 1977;49:927–933.
- Santiago TV, Edelman NH. Opioids and breathing. *J Appl Physiol* 1985;59:1675–1685.
- Sarton E, Teppema LJ, Olivier C, Nieuwenhuijs D, Matthes H, Kieffer BL, Dahan A. The involvement of the μ -receptor in ketamine-induced respiratory depression and antinociception. *Anesth Analg* 2001;93:1495–1500.
- Scamman FL, Ghoneim MM, Korttila K. Ventilatory and mental effects of alfentanil and fentanyl. *Acta Anaesthesiol Scand* 1984;28:63–67
- Scheinin M, Karhuvaara S, Ojala-Karlsson P, Kallio A, Koulu M. Plasma 3,4-dihydroxyphenylglycol (DHPG) and 3-methoxy-4-hydroxyphenylglycol (MHPG) are insensitive indicators of α_2 -adrenoceptor mediated regulation of norepinephrine release in healthy human volunteers. *Life Sci* 1991;49:75–84.
- Scholtz J, Steinfath M, Schulz M. Clinical pharmacokinetics of alfentanil, fentanyl and sufentanil. *Clin Pharmacokinet* 1996;31:275–292.
- Scott JC, Ponganis KV, Stanski DR. EEG quantization of narcotic effect: the comparative pharmacodynamics of fentanyl and alfentanil. *Anesthesiology* 1985;62:234–241
- Scott JC, Stanski DR. Decreased fentanyl and alfentanil dose requirements with age. A simultaneous pharmacokinetic and pharmacodynamic evaluation. *J Pharm Exp Ther* 1987;240:159–166.
- Seitz W, Lübke N, Fritz K, Sybrecht G, Kirchner E. Einfluss von tramadol auf die ventilatorische CO₂-antwort und den Mundokklusionsdruck. *Anaesthesist* 1985;34:241–246.
- Shafer SL, Varvel JR. Pharmacokinetics, pharmacodynamics and rational opioid selection. *Anesthesiology* 1991;74:53–63.

- Silvasti M, Rosenberg P, Seppälä T, Svartling N, Pitkänen M. Comparison of analgesic efficacy of oxycodone and morphine in postoperative intravenous patient-controlled analgesia. *Acta Anaesth Scand* 1998;42:576–580.
- Smith GM, Egbert LD, Markowitz RA, Mosteller F, Beecher HK. An experimental pain method sensitive to morphine in man: the submaximum effort tourniquet technique. *J Pharm Exp Ther* 1966;154:324–332.
- Soliman MG, Brindle CF, Kuster G. Response to hypercapnia under ketamine anaesthesia. *Can Anaesth Soc J* 1975;22:486–494.
- Taborsky GJ Jr, Halter JB, Porte D Jr. Morphine: dual effects on plasma catecholamines. *Endocrinology* 1981;109:319–321.
- Taittonen MT, Kirvelä OA, Aantaa R, Kanto JH. The effect of clonidine or midazolam premedication on perioperative responses during ketamine anesthesia. *Anesth Analg* 1998;87:161–167.
- Takala J, Keinänen O, Väisänen P, Kari A. Measurement of gas exchange in intensive care: Laboratory and clinical validation of a new device. *Crit Care Med* 1989;17:1041–1047.
- Takki S, Tammisto T. A comparison of pethidine, piritramide and oxycodone in patients with pain following cholecystectomy. *Anaesthesist* 1973;22:162–166.
- Tarkkila P, Tuominen M, Lindgren L. Comparison of respiratory effects of tramadol and pethidine. *Eur J Anaesth* 1998;15:64–68.
- Thompson PI, Joel SP, John L, Wedzicha JA, Maclean M, Slevin ML. Respiratory depression following morphine and morphine-6-glucuronide in normal subjects. *Br J Clin Pharmacol* 1995;40:145–152.
- Tobin MJ, Chadha TS, Jenouri G, Birch SJ, Gazeroglu HB, Sackner MA. Breathing patterns. 1. Normal subjects. *Chest* 1983;84:202–205.
- Traber DL, Wilson RD, Priano LL. Differentiation of the cardiovascular effects of CI-581. *Anesth Analg* 1968;47:769–777.
- Tulla H, Takala J, Alhava E, Hendolin H, Manninen H, Kari A. Breathing pattern and gas exchange in emergency and elective abdominal surgical patients. *Int Care Med* 1995;21:319–325.
- Tweed WA, Minuck M, Mymin D. Circulatory responses to ketamine anesthesia. *Anesthesiology* 1972;37:613–619.
- Valta P, Takala J, Foster R, Weissman C, Kinney JM. Evaluation of respiratory inductive plethysmography in the measurement of breathing pattern and PEEP induced changes in lung volume. *Chest* 1992;102:234–238.
- Vatner SE, Marsh JD, Swain JA. Effects of morphine on coronary and left ventricular dynamics in conscious dogs. *J Clin Invest* 1975;55:207–217.
- Vickers MD, O'Flaherty D, Szekeley SM, Yoshizumi J. Tramadol: pain relief by an opioid without depression of respiration. *Anaesthesia* 1992;47:291–296.
- Waldhoer M, Bartlett SE, Whistler JL. Opioid receptors. *Annu Rev Biochem* 2004;73:953–90.
- Wallenstein MC. Biphasic effects of morphine on cardiovascular system of the cat. *Eur J Pharmacol* 1979;59:253–260.

- Warner DO, Warner MA, Ritman EL. Human chest wall function while awake and during halothane anesthesia. *Anesthesiology* 1995;82:6–19.
- Warner MA, Hosking MP, Gray JR, Squillace DL, Yunginger JW, Orszulak TA. Narcotic-induced histamine release: a comparison of morphine, oxymorphone and fentanyl infusions. *J Cardiothor Vasc Anesth* 1991;5:481–484.
- Watson HL, Poole DA, Sackner MA. Accuracy of respiratory inductive plethysmographic cross-sectional areas. *J Appl Physiol* 1988;65:306–308.
- Weissman C, Askanazi J, Milic-Emili J, Kinney JM. Effect of respiratory apparatus on respiration. *J App Physiol* 1984; 57: 475–80.
- Welchew EA, Hoskin J. Patient-controlled postoperative analgesia with alfentanil. *Anaesthesia* 1985;40:1172–1177.
- Westmoreland CL, Sebel PS, Gropper A. Fentanyl or alfentanil decreases the minimum alveolar anesthetic concentration of isoflurane in surgical patients. *Anesth Analg* 1994;78:23–28
- White PF, Way WL, Trevor AJ. Ketamine- its pharmacology and therapeutic uses. *Anesthesiology* 1982; 56: 119–36.
- White PF, Coe V, Shafer A, Sung M-L. Comparison of alfentanil with fentanyl for outpatient anesthesia. *Anesthesiology* 1986;64:99–106
- Withington DE, Patrick JA, Reynolds F. Histamine release by morphine and diamorphine in man. *Anaesthesia* 1993;48:26–29.
- Woestenborgh R, Stanski D, Scott J, Heykants J. Assay methods for fentanyl in serum: gas-liquid chromatography versus radioimmunoassay. *Anesthesiology* 1987;67:85–90.
- Yamatodani A, Fukuda H, Wada H, Ivaeda T, Watanabe T. High-performance liquid chromatographic determination of plasma and brain histamine without previous purification of biological samples: cation-exchange chromatography coupled with post-column derivatization fluorometry. *J Chromatogr* 1985;344:115–123;.
- Yamatodani A. Assay of histamine and its metabolites in the brain. In: Watanabe T, Wada H, eds. *Histaminergic Neurons: morphology and function*. Boca Raton: CRC press, 1991:35–51.
- Zelis R, Mansour EJ, Capone RJ, Mason DT. The cardiovascular effects of morphine. *J Clin Invest* 1974;54:1247–1258.